1,2,4-TRIAZOLE-ALDEHYDES

by

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Contents.

Introduction.

INTRODUCTION.

Although many C-aldehydes of azoles and azines, including those of 1,2,3-triazoles, are known and readily obtainable, free aldehydes derived from 1,2,4-triazole do not appear to have been isolated previously. The main aim of the work submitted in this thesis was the synthesis of such 1,2,4-triazole-C-aldehydes.

Frerichs and Beckurts (26) isolated the phenylhydrazone of 1-phenyl-5-hydroxy-1,2,4-triazole-3-aldehyde from the complex mixture produced by reaction of phenylhydrazine with chloroacetylurethane or chloroacetylurea, but did not prepare the aldehyde itself. Parkes (58) prepared the 2,4,-dinitro-phenylhydrazone of O (or N)-acetyl-3-hydroxy-1,2,4-triazole-5-aldehyde. The crude free aldehyde was formed by ozonolysis of the corresponding 5-styryl compound, followed by treatment with Adams' catalyst; but it could not be obtained pure.

Apart from these cases, 1,2,4-triazole-C-aldehydes or their derivatives have not been noted in the literature.

The chemistry of the 1,2,4-triazoles has recently been reviewed (66), but relatively little is known when compared with the chemistry of other N-heteroaromatic series. A preliminary study of the properties of the 1,2,4-triazoles suggested that the aldehydes might not be prepared as readily as in some other series.

A brief summary is therefore given of the types of reaction which 1,2,4-triazoles might be expected to undergo, with reference to what is known of the electron distribution in the nucleus. This is compared with observed reactivity, or

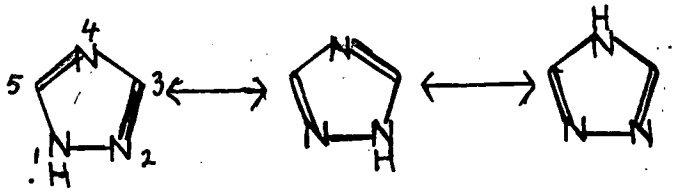
otherwise, in the few specific cases which have been described or studied. From this, limitations imposed by the intrinsic properties of the nucleus could be taken into account, to some extent, in seeking the course of reaction most likely to yield the desired compounds. Unfortunately, few quantitative measurements are available. Several 1,2,4-triazole-aldehydes have been obtained; and observations made of the properties of the 1,2,4-triazoles during the course of this work, do, in general, agree with what was expected.

T h e C h e m i s t r y

of the
1,2,4-triazoles.

The Chemistry of the 1,2,4-triazoles.

1,2,4-triazole (I) is classified as $\alpha\pi$-excessive-N-heteroaromatic compound, as it contains a five-membered ring, and at least one nitrogen atom in an electron-releasing setting (=CH-NH-).



(I)

π-deficient-N-heteroaromatics, such as pyridine, generally have a six-membered ring, and contain a nitrogen atom in an electron-attracting setting (=CH-N=).

In the case of (I) the position is complicated by the presence of one electron-releasing system, and two electron-attracting ones, which would reduce the π-excessive nature. Unfortunately the exact extent is not known. In this connection Albert (1) states: " the electron-releasing power of nitrogen in =CH-NH-CH= greatly exceeds the electron-attracting power of nitrogen in =CH-N=CH- , because pyrazole and iminazole behave as π-excessive substances, although less so than pyrrole. Further addition of doubly bonded nitrogen atoms must further diminish the electron-excessive character of five-membered rings, but information is too scanty to pronounce on the extent."

As far as direct substitution on a nuclear carbon atom is concerned the 1,2,4-triazole nucleus is in a particularly unfavourable position. The two electron-attracting groups present, largely neutralise the effect of the electron-

releasing group. This latter makes the other π-excessive heteroaromatics, pyrrole, pyrazole and iminazole, particularly reactive towards electrophilic substitution, but this is not so with 1,2,4-triazole. On the other hand the two electron-attracting groups are apparently not sufficiently powerful to overcome the effect of (=CH-NH-), and activate the nuclear carbon atoms towards attack by nucleophilic reagents. In agreement with this, no cases of nucleophilic substitution in the 1,2,4-triazole series are known.

Nucleophilic exchange should be encouraged by the presence of two doubly bonded ring nitrogen atoms, but attempts to replace C-halogen or C-mercapto groups by others such as ethoxy or hydroxy, have not been successful (34,50). 3-chloro-1,2,4-triazole is stable to treatment with fuming nitric acid or nascent hydrogen, but 3-bromo or 3-iodo-1,2,4-triazole are decomposed by both these reagents (50). C-amino-1,2,4-triazoles diazotise normally, and the diazo group can be replaced by -Cl or -Br. However, it was not found possible to introduce the -C≡N or -CH=NOH (cf.13) groups in this way, under the conditions tried (Section D, Ib, v).

The degree of reactivity of 1,2,4-triazole towards electrophilic substitution, compared with that of benzene and pyridine, is not known. Some indications might be given by comparing rates of nitration, sulphonation or halogenation at high temperatures, but the existing information is limited and conflicting.

That the 1,2,4-triazole nucleus is still somewhat π-excessive is suggested by its undergoing the indophenine reaction (1), by the reported direct introduction of the hydroxymethyl group (40), and by the nitration of 3-hydroxy-

1,2,4-triazole (50). In all other cases studied benzene substituted more readily than (I). 1,2,4-triazoles did not undergo the Reimer-Tiemann reaction; were not successfully chloromethylated, and gave no aldehydes on treatment with N-methyl-formanilide or dimethyl formamide and phosphorus oxychloride. (Section D, Ia). 1,2,4-triazoles do not undergo the Friedel-Crafts reaction, and no cases of sulphonation have been reported. That this nucleus may be less active than benzene to electrophilic substitution is also suggested by the smooth nitration of 1-phenyl-1,2,4-triazole-3-carboxylic acid on the benzene ring, without any apparent attack on the triazole ring (16). Similarly it was found that 3-p-nitrophenyl-1,2,4-triazole was the only product isolated on nitration of 3-phenyl-1,2,4-triazole. (Section D, Ib, viii). Neither (I) nor 3-methyl-1,2,4-triazole was nitrated under the same conditions. However, 2 or 4-phenyl iminazole are nitrated first on the benzene ring, even though iminazole is usually regarded as being rather π-excessive (29,68). The effect may be partly due to attraction of electrons from the heterocyclic nucleus by the benzene ring, and partly due to immonium-salt formation on the >NH group, where this is present.

Little is known of the direct halogenation of the 1,2,4-triazoles, apart from the statement that 3-hydroxy or 3-halogeno-derivatives, as solids or in solution, were not substituted by free bromine (50). (I) was recovered unchanged when treated with bromine and conc. sulphuric acid up to 100°C. However, when (I) was treated with bromine in carbon tetrachloride, in the presence of iron filings and iodine, a deep red tar formed readily, and no 1,2,4-triazole was recovered. (Section D, Ib, ii). This product seemed a complicated mixture and was not further

studied. This brief observation suggests that (I) may in some respects resemble 1,2,3-triazole, which is rather readily halogenated (37).

The physical and chemical properties of many acyl-azoles have been studied and compared (7,56,66,79). A gradation in the properties of the N-acetyl-derivatives was generally observed from pyrrole, through the diazoles, then the triazoles to tetrazole. (I) may be directly acetylated on a nitrogen atom, with acetic anhydride, the product being the same as that from acetyl chloride and the sodium or potassium salt of 1,2,4-triazole (7). This 1 (or4)-N-acetyl-1,2,4-triazole is easily hydrolysed, and is a strong acetylating agent, resembling N-acetyl-iminazole rather than N-acetyl-pyrrole or N-acetyl-pyrazole. C-acetylation does not occur with 1,2,4-triazoles.

No substitution was detected in attempted reactions between (I) and diphenylformamidine, or chloralhydrate and zinc chloride. Nor could a diazonium group be introduced, even using a method by which this group may often be successfully linked to a deactivated nucleus (82).

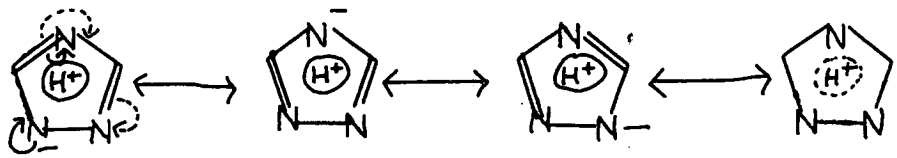
In an attempted reaction between (I) and ethyl magnesium bromide a heavy white precipitate, possibly a =N-Mg-Br derivative, was obtained. However, on attempted reaction of this product with benzoyl chloride, followed by hydrolysis, (I) was recovered unchanged. (Section D, Ib).
These examples show the decreased electron availability on a carbon atom, of 1,2,4-triazole, as compared to that in pyrrole, pyrazole or iminazole.

The 1,2,4-triazole nucleus is stable to oxidation and reduction, and substituents may be oxidised or reduced with-

out affecting the nucleus. It is inert towards lithium aluminium hydride, and to sodium and liquid ammonia (22).

(I) is amphoteric, being a stronger acid (acidic pK_a=10.1) than pyrrole, pyrazole or iminazole, and a weaker base (basic pK_a=2.30) than the last two (1). It can exist in either a cationic or an anionic form.

Although the formula of 1,2,4-triazole is conveniently written as if the =NH hydrogen atom were localised (I), it is generally accepted that the true structure is a resonance hybrid, and the nucleus has high aromatic character. The formula, has for example, also been written (66):



The high dipole moment observed (3.17μ) (39) shows that (I) is electrically asymmetrical, and the first three forms shown are probably not of equal importance. There appears to be an appreciable contribution from the resonance form that has the negative charge more closely associated with the nitrogen atom in the 4-position. Unfortunately this dipole moment, and that for 3-hydroxy-1,2,4-triazole (3.30μ), were obtained using dioxan as solvent, which often gives high results in cases where hydrogen bonding can occur (1,39). Values for 1-phenyl and4-phenyl-1,2,4-triazole were 2.68μ and 5.63μ, respectively, both determined in benzene. These are high values for azole derivatives.

Melting and boiling points of N-unsubstituted-azoles, including 1,2,4-triazoles, are often much higher than might be expected from consideration of their low molecular weights. alone. This is related to their dipole moments and amphoteric properties, which result in considerable intermolecular bonding. (39).

	M.P. °C	B.P. °C	Dipole moment (B in benzene (D in dioxan
Benzene	5.5	80	0
Pyrazole	70.o	185	1.47 B
1,2,3-triazole	23.o	203	1.77 B
Iminazole	90.o	256	4.84 D,3.84 B (inf.di
1,2,4-triazole	121.o	260	3.17 D
Tetrazole	156.o	---	5.11 D

On the other hand N-alkyl or N-aryl-azoles, where this effect cannot occur,generally have lower melting and boiling points than the corresponding C-substituted compounds (52). This may be observed with the 1,2,4-triazoles:

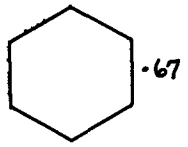
	M.P. °C	B.P. °C/760 mm
1-methyl-triazole	<10	178
3-methyl-triazole	96	265
4-methyl-triazole	90	---
1-phenyl-triazole	47	266
3-phenyl-triazole	119	---
4-phenyl-triazole	121	---

N-unsubstituted 1,2,4-triazoles are very soluble in polar solvents,but only slightly in non-polar ones.

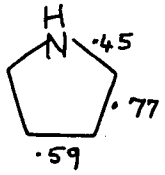
Not much is known of the extent of tautomerism in the C-hydroxy,C-mercapto or C-amino-1,2,4-triazoles;but the last behave like normal aromatic amines.That some tautomerism

does occur with the hydroxy-triazoles was suggested by studies of their ultra-violet spectra (6,58). 3-SH groups may be removed by treatment with Raney nickel, or hydrogen peroxide (39), or by nitric acid oxidation (40).

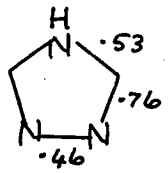
Unlike with benzene, where all bond lengths are equal (i), there is some tendency towards localisation of double bonds in most N-heteroaromatic nuclei. The greater this tendency the greater the likelihood of addition reactions, as with pyrrole (ii) (1,47). In (I), which shows a high degree of aromaticity, such an effect might be reduced; and 1,2,4-triazoles do not normally undergo addition reactions. However, (I) does undergo conjugate addition with some α-β-unsaturated carbonyl compounds (92). In the case of the 1 or 4-substituted-1,2,4-triazoles approximate calculations (55) suggest that there is some double bond localisation in these cases (iii; iv).



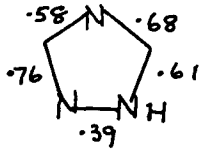
(i)



(ii)

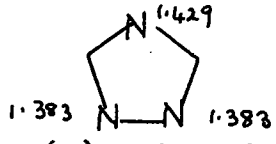


(iii)

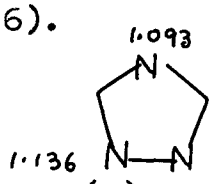


(iv)

Several calculations have been made of π-electron densities for 1,2,4-triazole. Unfortunately the values obtained vary considerably with the different parameters (h) used, and are thus difficult to interpret (1,5,6,55,66,95). Among the most reliable are those for neutral triazole (1), and the triazolate anion (2) (5,6).



(1) ; h= +1



(2) ; h = $-(\frac{1}{3})$

Other calculations, using differing parameters, have been made for the neutral molecule (5,55,95); and for the anion (5). All results obtained in the latter case showed that $N_{(1)}$ and $N_{(2)}$ were more nucleophilic than $N_{(4)}$, as might be expected by the formation of 1-alkyl derivatives in the reaction of sodium triazolate with alkyl iodides.

In the neutral molecule the electron density is lowest on $N_{(1)}$ and $N_{(2)}$, which are thus the centres attacked by diazomethane. On the other hand, reactions requiring a high electron density, such as quaternisation of a tertiary nitrogen atom with alkyl halides, take place preferentially at $N_{(4)}$ not $N_{(1)}$ (20).

As there seemed little possibility of introducing a substituent directly into the preformed 1,2,4-triazole nucleus, the synthesis of 1,2,4-triazole-C-aldehydes seemed largely dependent on suitable reactions of groups already in the nucleus.

Many aromatic and heterocyclic aldehydes may be readily obtained from side chain methyl groups. However, no reagent was found to oxidise a C-methyl-1,2,4-triazole to an aldehyde; even chromyl chloride was ineffective. Methyl-triazoles seemed unaffected by some oxidising agents like selenium dioxide, manganese dioxide, sodium persulphate, or lead tetra-acetate. With other oxidising agents, like potassium permanganate or chromic acid, the 1,2,4-triazole-C-carboxylic acids formed, usually accompanied by much tar.

C-methyl groups in 1,2,4-triazoles are not known to couple with aldehydes or amines. When such methyl groups are activated by quaternisation of a nitrogen atom in the triazole nucleus, it has been found possible to couple them with some reagents, to form cyanine dyes (20); but vigorous reaction conditions

were needed, and yields were poor. 1 (or 4)-trityl-3-methyl-1,2,4-triazole was quaternised with methyl iodide, and the product was reacted with p-nitroso-dimethylaniline, in an attempt to form a Schiffs' base (96). Under the conditions used, however, no such condensation was detected in this case.

Discussion.

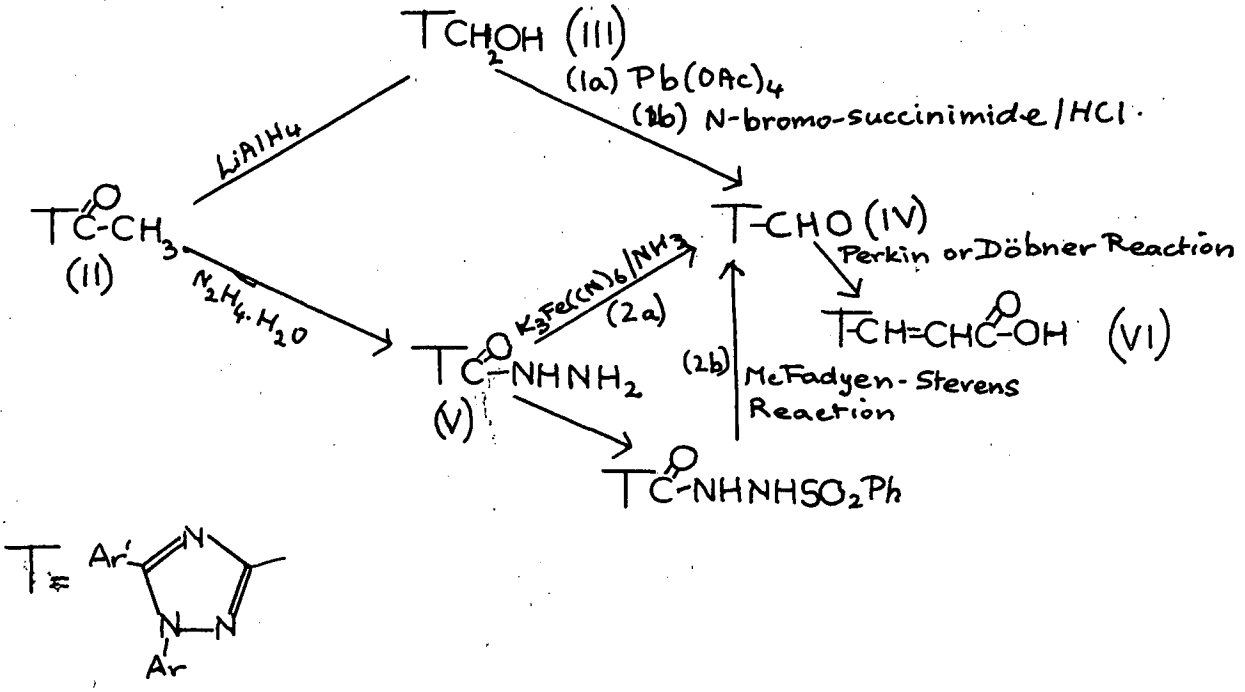
Discussion of the Project, and Results obtained.

In view of the difficulties described in the previous section the synthesis of 1,2,4-triazole-C-aldehydes from the corresponding carboxylic acids, or compounds derived from them, seemed the most promising route. However, this had been limited by the relative inaccessibility of these acids, associated with their instability. They decarboxylate readily, even under mild esterification conditions, and it has not yet been found possible to isolate any of the acid chlorides, even if preparation was attempted in the presence of dimethylformamide (cf. 17). The Rosenmund reduction of acid chlorides was therefore not applicable.

A more satisfactory method of synthesis of the 1,2,4-triazole-3-carboxylic acids, and their derivatives, seemed desirable. For this reason the rearrangement of 2-phenyl-4-phenylazo-oxazolin-5-one in alkaline solution, to derivatives of 1-H-1,2,4-triazole, reported by Sawdey (74), has been investigated. Its scope has been extended to make readily accessible many 1,5-diaryl-1,2,4-triazole-3-carboxylic acids, their esters, hydrazides, amides, and other related derivatives. These derivatives can all be obtained directly, or by cyclisation of acylic intermediates, without isolation, or even formation, of the unstable acids. Six new azlactones were made as starting materials.

Several of these 1,2,4-triazole-3-carboxylic acid derivatives have been converted, by standard methods, to 1,2,4-triazoles containing other functional groups, such as $-CO-N_3$, $-CH_2NHPh$, $-CO-NH-NH-SO_2Ph$ and $-CH_2OH$. In the last case a series of seven 1,5,-diaryl-3-hydroxymethyl-1,2,4-triazoles (III) was made by lithium aluminium hydride reduction of the corresponding methyl esters (II). One of these alcohols (III, Ar-=Ar'-=Ph-) was isolated in two forms, one stable and one labile.

From studies on these, now readily available, compounds, two practicable methods of synthesising 1,5-diaryl,1,2,4-triazole-3-aldehydes (IV) or their derivatives, have been found. One was the oxidation of the corresponding alcohols (III) with lead tetraacetate in benzene, to the aldehydes (IV) in yields of 10-70%. In the alternative Kalb-Gross procedure (41) the 1,2,4-triazole-3-carboxylic acid hydrazides (V), prepared either from the esters (II) and hydrazine hydrate, or directly by the Sawdey rearrangement, were treated with potassium ferricyanide and ammonia in aqueous ethanol, to afford aldehydes or their derivatives in yields of 10-35%.

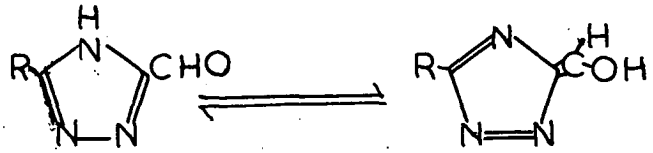


In addition, the McFadyen Stevens procedure (49) or, more satisfactorily, its modification by Newman and Caflisch (54) using powdered glass, gave traces of aldehydes, as derivatives. Aldehydes were also obtained by treatment of the alcohols (III) with N-bromo-succinimide, followed by acid hydrolysis.

The products were usually detected and estimated as their 2,4-dinitrophenylhydrazones, or, less frequently, as other derivatives.

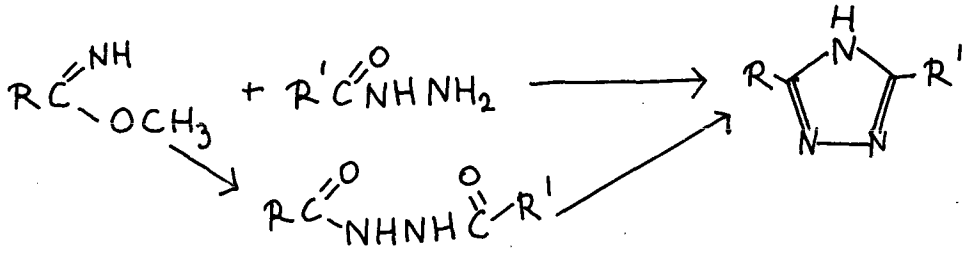
Seven 1,5-diaryl-1,2,4-triazole-3-aldehydes (IV) were isolated in the free state, using a modified method for the decomposition of their Girard-T derivatives. They are fairly stable when pure, undergo normal aldehyde reactions, and form the usual derivatives. They may be converted to the substituted acrylic acids (VI) by the Perkin reaction, or preferably by the Döbner reaction.

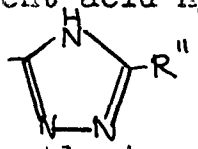
All the 1,2,4-triazole-C-aldehydes described above have a substituent on a ring nitrogen atom. The synthesis of 1,2,4-triazole-C-aldehydes with no such substituent was expected to be more difficult, due to interference by the -NH-group, both in the preparation, and in its making the product susceptible to polymerisation. Any such product might too, not have typical aldehyde properties, due to tautomerism of the type shown:



Such aldehydes have not yet been successfully isolated in the free state. However, several of the corresponding acetals have been made; and these have been converted to other aldehyde derivatives, by simultaneous acid hydrolysis, and precipitation with suitable reagents.

These 5-substituted-1,2,4-triazole-3-aldehyde dimethyl acetals were synthesised by condensation of imino-ethers with a suitable carboxylic acid hydrazide, in methanol, as shown (cf. 64).



This reaction has also been used to synthesise 5-substituted-1,2,4-triazoles with other functional groups in the 3-position. Thus, by the use of different acid hydrazides, triazoles with R'= $-CH_2OCH_3$, $-CH_2CN$ and  have been made.

In some cases the triazoles formed directly, in others intermediate amidrazones formed first, but were readily cyclised. Occasionally ring closure of the amidrazone did not occur. Due to the instability of the free imino-ether required, 5-unsubstituted-1,2,4-triazoles (R=H-) could not be made in this way.

Some preliminary studies have been made of the spectra of these new aldehydes, and other 1,2,4-triazoles, both in the ultra-violet and infra-red regions. This is part of a current study of the spectra of the 1,2,4-triazoles in general, notably in the infra-red. Only a brief discussion is therefore given of this aspect of the work (Section E).

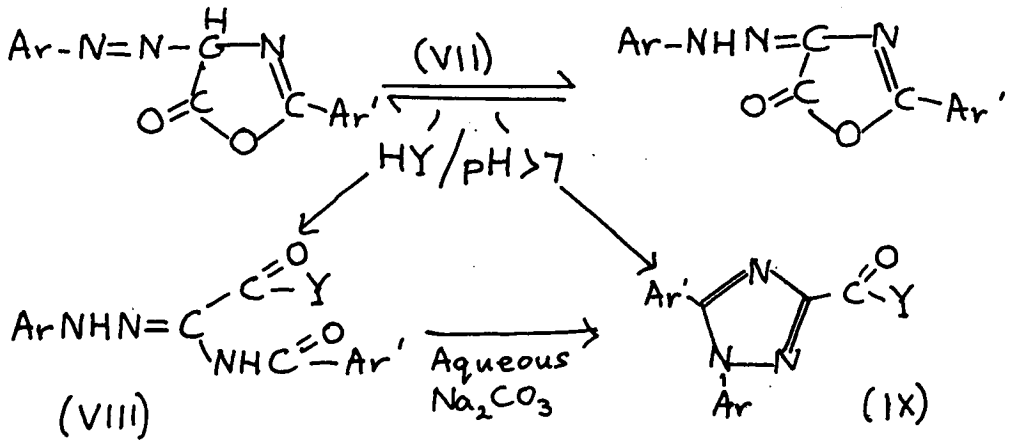
Diacylamines are used as starting materials for many 1,2,4-triazole syntheses (4,5,6,7). Early in the project studies were made of their chemistry and reactions, notably the preparation of their N-bromo derivatives. This work is described in Appendix B.

Section A.

The rearrangement of 4-arylazo-2-aryl-oxazolin-5-ones to derivatives of 1-H-1,2,4-triazoles.

Introduction.

Buskov (44) described the preparation of 4-arylazo-2-phenyl-oxazolin-5-ones (VII; Ar'= -Ph; Ar=-Ph, p-nitrophenyl, p-tolyl-) by the reaction of hippuric acid in acetic anhydride with diazotised amines, or the corresponding diazoamino compounds. For the substances obtained on heating the first two with methanolic ammonia, he claimed the acyclic structure (VIII; Ar'=Ph; Ar=-Ph, p-nitrophenyl; Y= $-NH_2$).



Subsequently Bawdey (74) showed that (VII, Ar=Ar'=-Ph) actually rearranges to the amide of 1,5-diphenyl-1,2,4-triazole-3-carboxylic acid (IX, Ar=Ar'=-Ph, Y=$-NH_2$); the acid itself being obtained from the rearrangement of (VII) with methanolic potassium hydroxide.

The azlactones described by Kuskov have been prepared, by Sawdey's method, in addition to six new ones (Table I); and the course of their rearrangements with several basic reagents has been investigated. In all cases methanol was used as the solvent.

Outline of Results obtained.

The final stable product of the rearrangement of the azlactone(VII) in basic solution was, in most cases, found to be the 1,2,4-triazole-3-carboxylic acid or derivative(IX), in agreement with Sawdey's work. However, in some cases, but not when (Ar-=Ar'-=-Ph), light yellow acyclic intermediates (VIII), of a type postulated by Kuskov, were obtained first. These generally required heating with dilute aqueous sodium carbonate to cyclise to the colorless 1,2,4-triazoles (IX). In some cases cyclisation failed (e.g. VIII; Ar-=m-tolyl or 2-naphthyl-, Ar'-=-Ph; Y=$NHNH_2$-). Resistance to cyclisation occasionally led to side reactions. Thus attempts to force cyclisation with alkali, when (Ar=o-tolyl) resulted in the formation of some o-cresol, as by-product.

The rearrangement did not occur in solutions acid to litmus. In aqueous methanol, made just alkaline with sodium or potassium carbonate or hydroxide, formation of esters (IX; Y=-OCH_3) is favoured initially. At higher pH the yield of the carboxylic acid anion (IX; Y=-O^-) increased rapidly, due to the sensitivity of the esters to hydrolysis. Acyclic ester intermediates (VIII; Y=-OCH_3), but not the corresponding acyclic acids, have been obtained when (Ar-=o- or m-tolyl; Ar'-=-Ph)

With ammonia or hydrazine the final products were the expected 1,2,4-triazole amides or hydrazides, respectively (IX; Y=-NH_2 or -$NHNH_2$). The 1,2,4-triazole-amides generally formed directly, only two doubtful intermediates being obtained (possibly VIII, Ar-=o-or m-tolyl, Ar'-=Ph-; Y=-NH_2). In the reaction of(VII) with hydrazine, however, the initial formation of intermediates (VIII; Y=-$NHNH_2$), was the rule

except in the case (Ar-=Ar'-=-Ph). From the reaction of (VII;Ar-=Ar'-=Ph-) with the primary amines,aniline or ethylamine,the corresponding secondary amides were formed (IX; Ar-=Ar'-=Ph-; Y=-NHPh or $-NHCH_2CH_3$).The rearrangement did not occur with secondary or tertiary amines, esters being obtained if the reaction mixture was otherwise made sufficiently alkaline to cleave the azlactone.

(VII; Ar-=Ar'-=Ph-) reacted smoothly with semicarbazide/ sodium bicarbonate,to yield (IX; Ar-=Ar'=Ph-; Y=-NHNHCONH$_2$). This same compound formed from the action of sodium cyanate on the corresponding 1,2,4-triazole-3-carbox hydrazide, in glacial acetic acid; thus confirming the structure.
No similar reaction was proved between (VII; Ar'-=Ph-; Ar-= p-tolyl-) and semicarbazide,in aqueous methanol,the only product isolated being the triazole carboxylic acid methyl-ester.Some reaction occured between semicarbazide and (VII; Ar'-=Ph-;Ar-=p-methoxy-phenyl-),but the product was a crude mixture,which was not characterised.

The 1,2,4-triazole esters (IX; Y=-OCH_3) were readily converted to the hydrazides (IX;Y=-$NHNH_2$),identical with those obtained by direct rearrangement of (VII).However,the ester (IX;Ar-=Ar'-=Ph-; Y=-OCH_3) did not react directly with aniline or semicarbazide,to give the corresponding 3-substituted-1,2,4-triazoles,obtained by the rearrangements described.

The esters (II),with the exception of (Ar-=Ph-;Ar'-=p-nitro-phenyl-),were readily reduced by litium aluminium hydride in ether,to the alcohols (III).The reduction of the acyclic esters (VIII;Ar'-=Ph-;Ar-= o-or m-tolyl-; Y=-OCH_3), gave the expected cyclic alcohols (III).

Reduction of (II;Ar-=Ar'-=Ph-) in this manner,afforded either the stable alcohol (IIIaB),m.p.154° C.,or the labile isomer (IIIaA,Table III),m.p.133° C.A was readily converted to B,

by acidification or standing in solution. The UV absorption maximum of (IIIaA) at 261 mμ changed to that of (IIIaB) at 248 mμ, in methanol solution (see Section E). Both alcohols were colorless; they were oxidised to the same acid; and gave the same acetyl derivative. B was a monomer, with a molecular weight of about 250 (Rast). The hydrazides (V; Ar'-=Ph-; Ar-=Ph- or p-methoxy-phenyl-) were readily converted to the triazole acid azides, by treatment with nitrous acid.

The secondary amide (IX; Ar-=Ar'-Ph-; Y=-NHPh) was partly reduced with $LiAlH_4$ in ether to give the secondary amine. However, (IX; Ar-=Ar'-=Ph; Y=-$NHCH_2CH_3$ or -NH_2) were not reduced under the same conditions.

The azlactone (VII; Ar-=Ar'-=Ph-) did not react with diethylamine, urethane, thiosemicarbazide, guanidine, aminoguanidine or methylcarbazate. In all cases the only products isolated, if any, after long reaction in aqueous methanol, were the 1,2,4-triazole-acid or the methylester (IX; Ar-=Ar'=Ph-; Y=-O^- or -OCH_3).

The effects of substituents in the aryl groups on the rearrangement of (VII); and the influence of the basic reagent.

In all cases the rearrangement mentioned occured in aqueous methanol, under the influence of a suitable basic reagent HY. The nature of Y partially determined the stability of the intermediate; but the nature and position of substituents in the aryl groups in (VII), also had a marked effect in some cases.

No acyclic acid intermediate has been isolated, so it is possible that ester ring closure may occur before hydrolysis. Alternatively the acyclic acid anions (VIII; Y=-O$^-$) may be regarded as unstable, and as cyclising before they can be detected. Some of the acyclic esters are stable (VIII; Ar'-=Ph-; Ar-=o- or m-tolyl-), possibly due to steric hindrance or deactivation. The other acyclic esters tend to cyclise rather than hydrolyse in the presence of mild alkali; the yield of triazole -acid increasing sharply at higher pH. In the case of the reaction of (VII; Ar'-=Ph-; Ar-=2-naphthyl-) with methanolic alkali, only a little triazole acid was isolated, and much tar; no cyclic or acyclic ester was obtained. The conjugate acids of (IX; Ar-=p-nitro-phenyl-; Ar'-=Ph; Y=-O$^-$; or Ar-=Ph-; Ar'-=p-bromo-phenyl-; Y=-O$^-$) were not isolated pure, due to rapid decarboxylation and tar formation; but in both cases the esters were readily obtained.

In the rearrangement of (VII) with hydrazine hydrate no intermediate was isolated where (Ar-=Ar'=Ph-). For all other cases intermediates were obtained (Table II), which could not be purified due to instability; but could mostly be cyclised to 1,2,4-triazoles, with varying degrees of difficulty.

Where (Ar'-=Ph-) little qualitative difference could be noted with certainty between the case of cyclisation of the

hydrazide intermediates for (Ar-=p-tolyl-;p-methoxy-phenyl-; p-nitro-phenyl or p-bromo-phenyl-).Where (Ar-=o-tolyl-) cyclisation was slower ,but not markedly so;this presumably being a steric effect.Neither of the hydrazide intermediates (Ar'-=Ph-;Ar-=m-tolyl-or 2-naphthyl-) could be cyclised; only tars were obtained. This could be partly due to deactivation, by lowering the electron density at the point of ring closure; although steric effects may be important,especially in the latter case.

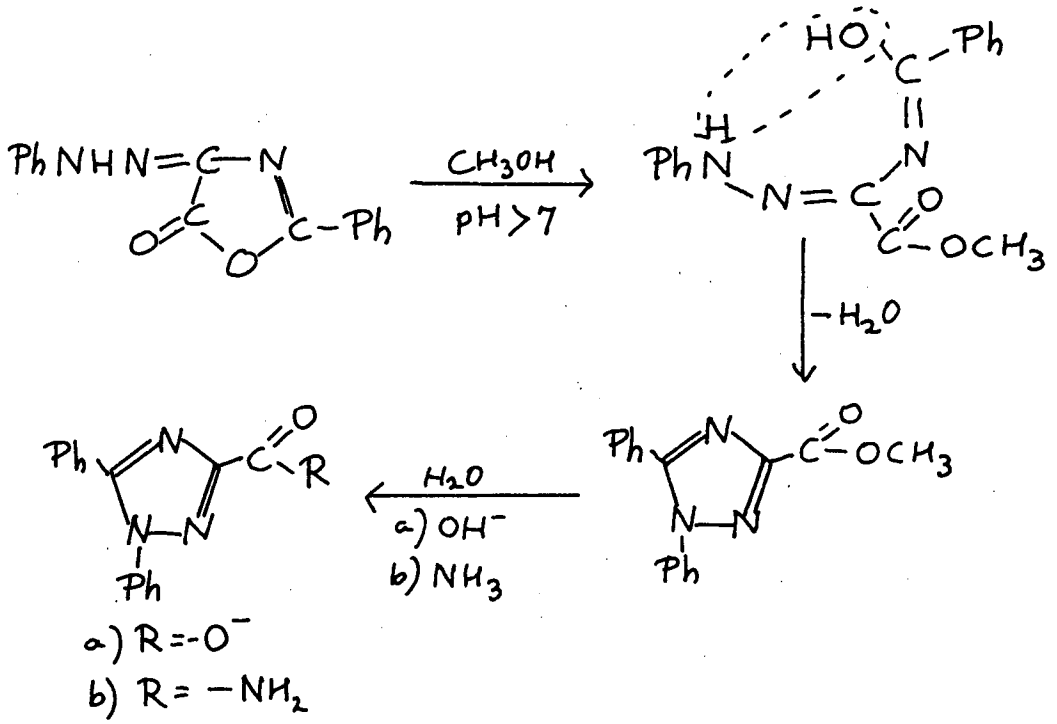
The other hydrazide intermediate (VIII;Ar-=Ph;Ar'-=p-bromo-phenyl-) was the most difficult to cyclise of those which gave any triazole acid hydrazide. A small amount was obtained on cyclisation with sodium bicarbonate; stronger alkalies giving only tars. This difference from its isomer is not clear; but in association with the instability of the triazole acid, suggests that a p-bromo-phenyl group in the 5-position may reduce the electron density in the triazole ring to a greater extent than one in the 1-position.

In the presence of ammonia(VII) generally gave the triazole amides directly.Neither of the two doubtful intermediates (VIII;Ar-=o- or m-tolyl-Ar'-=Ph-) was definitely characterised, but both resembled the equivalent hydrazide intermediates in properties.

A list of the probable intermediates isolated, with their properties , is given in Table II.

The Course of the Sawdey Rearrangement.

On the information available it was not possible to establish with certainty the course taken during the rearrangement described. Different routes may be followed, depending on the substituents present, the reagents used, and the pH, provided that this is >7. Sawdey (74) postulated the following mechanism, in the single case which he investigated (VII; Ar=Ar'=Ph) viz:



He thus suggested that the arylazo-azlactone first opened to the acyclic ester, by the action of the methanolic alkali; then cyclised to the 1,2,4-triazole-carboxylic acid ester, whichwas hydrolysed to the acid , or converted to the amide.

As the esters of 1,2,4-triazole-3-carboxylic acids are readily hydrolysed, and no triazole intermediate has been isolated, formation of the triazole acids, especially in strongly alkaline conditions, is in accordance with Sawdey's views.

Failure to isolate pure intermediates from reactions leading to the formation of 1,2,4-triazole amides, does not argue for or against this mechanism, in most of the examples. However, evidence now suggests that, in some cases at least, the side chain substitution occurs first, followed by subsequent ring closure. This would certainly seem so in the reaction of (VII; except when Ar-=Ar'-=Ph-) with hydrazine hydrate, where the isolation of acyclic acid hydrazides, definitely argues against the above mechanism. These intermediates were not esters, and had high melting points. As opposed to the colorless triazoles they were all colored, generally a shade of yellow; and the UV-spectra were different from those of the triazoles. In the one instance mentioned, however, which occured with no detectable formation of an acyclic intermediate, the ester may form first if the rearrangement was carried out with a reduced quantity of hydrazine hydrate.

The cyclisation of the acyclic esters (VIII; Ar'-=Ph-; Ar-=o- or m-tolyl-; Y=-OCH_3), in the course of their reduction with $LiAlH_4$, to form the corresponding hydroxymethyl-triazoles, is also unlikely to occur by Sawdey's mechanism.

In only two cases where an acyclic intermediate was not isolated could the rearrangement be shown unlikely to follow the postulated route. These were the reactions of (VII; Ar-=Ar'-=Ph) with aniline or semicarbazide, to give the triazoles directly. In neither case would these products form by direct reaction of the triazole ester with the basic reagent, under much stronger conditions than were used in the rearrangement.

In all other cases studied the observed results were in conformity with either reaction course, and no decision, either way, could be reached.

Section A.

Section A: Experimental.

1) 4-arylazo-2aryl-oxazolin-5-ones. (Table I).

These azlactones were made, essentially, by the method described by Sawdey (74), which was superior to preparation in aqueous solution (44).

A typical example was the preparation of 2-phenyl-4-p-methoxy-phenylazo-oxazolin-5-one (VII f).

A solution of p-anisidine (12.3g, $\frac{M}{10}$) in glacial acetic acid (75 ml) and conc. hydrochloric acid (22 ml), was cooled in an ice salt bath, and diazotised with amyl or isoamyl nitrite (13g). Freshly fused sodium acetate (20g) was added, followed by a freshly prepared solution of hippuric acid (20 g.) in acetic anhydride (80 ml); this latter being added as rapidly as possible, with good stirring, keeping the temperature below 15° C., throughout the addition. The reaction mixture was then stood in a refrigerator at 0-4° C. The rate of precipitation of the product varied, generally being complete in 1-2 hours, but occasionally small amounts were still obtained after 1-3 days.

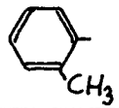
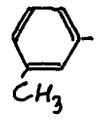
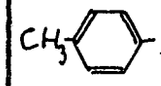
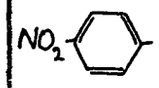
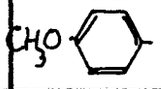
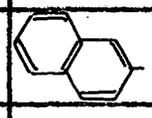
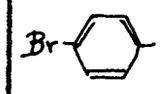
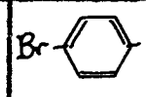
The crude product, containing much inorganic matter, was sucked dry on a Buchner funnel and was used directly for rearrangement experiments. Yields given are approximate ones, calculated on quantities of rearrangement products obtained. The azlactones were recrystallised from suitable solvents for analysis.

They are stable if kept in a dry atmosphere, but are unstable to heat or alkaline conditions.

In the preparation of (VII j) the hippuric acid was replaced by p-bromo-hippuric acid (m.p. 160-2° C.), synthesised from p-bromo-benzoylchloride and glycine, by the Schotten-Baumann method (23).

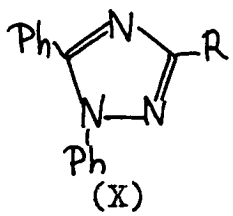
Analyses are not given for compounds which have been previously described in the literature.

TABLE I. 4-Arylazo-2-aryl-oxazolin-5-ones (VII).

Reference Number	Ar-	Ar'-	Crystals	m.p. °C. All with slight decomp.	Approx. yield %	Analysis: Found C	H	N%	Analysis: Theoretical C	H	N%
VIIa.	Ph	Ph-	Deep yellow needles from acetone	201-3	70	See Reference (44)					
VIIb.		Ph-	Orange crystals from benzene/petrol ether	161-2	30	68.6	4.7	14.9	$C_{16}H_{13}N_3O_2$ requires	68.8	4.7	15.1
VIIc.		Ph-	Orange needles or plates from benzene/ petrol ether	188-191	18	69.1	4.9	15.1	Ditto			
VIId.		Ph-	Orange plates from benzene	209-211	68	See ref.(44)					
VIIe.		Ph-	Orange-yellow powder from dioxan	314-7	30	See ref.(44)					
VIIf.		Ph-	Crimson plates from benzene	201-3	45	64.9	4.4	14.1	$C_{16}H_{13}N_3O_3$ requires	65.1	4.4	14.2
VIIg.		Ph-	Red plates from $CHCl_3$/ pet.ether	229-230	35	71.5	4.2	12.7	$C_{19}H_{13}N_3O_2$ requires	72.3	4.2	13.3
VIIh.		Ph-	Deep yellow needles from $CHCl_3$/pet.ether	247-8	40	52.4	2.9	11.6	$C_{15}H_{10}N_3O_2Br$ requires	52.3	2.9	12.2
VIIj.	Ph-		Deep yellow needles from $CHCl_3$/pet.ether	260-1	42	51.5	3.0	11.4	Ditto			

Petrol-ether used was boiling range 40-60 °C. Melting points were uncorrected.
light petroleum

2) Rearrangement undergone by 2-phenyl-4-phenylazo-oxazolin-5-one (VII a) to give products of the type:



(X)

a. R= -COOH
b. R= $-COCH_3$
c. R= $-CONHNH_2$
d. R= $-CONH_2$
e. R= -CONHPh
f. R= $-CONHCH_2CH_3$
g. R= $-CONHNHCONH_2$
h. R= $-CONHNHSO_2Ph$
j. R= $-CH_2NHPh$
k. R= $-CH_2Cl$

1,5-diphenyl-1,2,4-triazole-3-carboxylic acid (Xa) and its methylester (Xb).

(VIIa) was suspended in methanol (5-10 volumes), and a 10-20% solution of aqueous KOH was added slowly, with stirring, until the mixture was strongly alkaline. The reaction was completed by gentle heating for 5 minutes, the mixture concentrated slightly, diluted with water and cooled. Cautious acidification with conc. HCl gave the acid (Xa), m.p. 177-8°C. (decomp.) (15).

If the methanolic suspension of (VIIa) was treated with aqueous Na_2CO_3, or just sufficient aqueous KOH to give a pH 7-9, and was then boiled gently for 5-10 minutes, the only product isolated was the methyl ester (Xb) m.p. 158-9°C., identical with that described by Bladin (15) and Sawdey (74). At slightly higher pH values mixtures of the acid and ester formed; the proportion of the acid increasing with increase in pH. On acidification some tarry by-products may be obtained, probably due to the ready decarboxylation of the 1,2,4-triazole carboxylic acid.

It was confirmed that the product of the reaction of (VIIa) with aqueous ammonia in methanol was the 1,2,4-triazolecamide (Xd), as claimed by Sawdey (74), and not the acyclic compound (VIII, Ar-=Ar'-=Ph-; Y=-NH_2) as proposed by Ruskov (44).

(Xd) was not reduced by $LiAlH_4$ in ether to the corresponding amine; the reaction mixture yielding only unchanged starting material, and some red tar. Nor did (Xd) appear to undergo the Hofmann amide degradation to any useful extent, although traces of isocyanates could be detected.

1,5-diphenyl-1,2,4-triazole-3-carboxylic acid hydrazide (Xc)

(VIIa) heated for 2-3 minutes in methanolic suspension (5-10 vol.) containing an excess of 85% hydrazine hydrate, followed by partial evaporation of the alcohol, dilution with water and cooling, readily gave the triazole acid hydrazide (Xc). This recrystallised from benzene as white prisms, m.p. 185-6°C. (Found: C, 64.8; H, 5.0; N, 24.9. $C_{15}H_{13}N_5O$ requires C, 64.5; H, 4.7; N, 25.1%).

2.0 g (Xb) heated for 15 minutes in methanol solution, with 2 ml. 85% hydrazine hydrate, gave, on concentration and cooling, 1.9 g. (95%) white prisms, m.p. 185-6°C, identical with the previous product; thus confirming the structure of (Xc). This was important, as, theoretically, reaction of (VIIa) with hydrazine could give rise to more than one product.

Preparation of (Xh), the benzene sulphonyl derivative of (Xc): 3.2 g (Xc.) in dry pyridine (15 ml) was cooled in an ice bath, and benzene sulphonyl chloride (2.1 g, 1:1) was added dropwise, with good stirring, over 15 minutes. After 30 minutes at room temperature water was added dropwise, the precipitate which formed being filtered off and washed with water. Charcoaling and recrystallisation from chloroform/petrol ether gave (Xh, 2.7 g, 56%), as white, fluffy crystals, m.p. 239-241°C (Found : C, 60.2, H, 4.3; N, 16.0 . $C_{21}H_{17}N_5O_3S$ requires C, 60.1; H, 4.1; N, 16.7 %).

The crystals were insoluble in water and ether, and almost so in propanol, ethanol and benzene.

The 1,2,4-triazole secondary amides (Xe) and (Xf).

(Xf) To a suspension of 2g crude azlactone (VIIa) in 50 ml. methanol and 5 ml. water was added 4g. ethylamine.HCl, followed by sufficient sodium bicarbonate to make the mixture just alkaline to litmus. Further small amounts of ethylamine.HCl and $NaHCO_3$ were added over 1 hour, with pH 7-8; and the mixture was kept at room temperature overnight. Concentration to 30 ml. and dilution with water gave 1.4 g. product, as white prisms or plates from aqueous methanol, m.p. 195-6°C (Xf). (Found: C, 70.6; H, 5.7; N, 19.1 $C_{17}H_{16}N_4O$ requires C, 69.8; H, 5.5; N, 19.2%).

Attempted reduction of (Xf) with $LiAlH_4$ in ether was unsuccessful, the amide being recovered unchanged.

(Xe) Refluxing (VIIa) with excess aniline in methanol for 1 hour, cooling, filtration and washing with water, gave a crude yellowish powder. Charcoaling and recrystallisation from chloroform/petrol ether gave white crystals (Xe), m.p. 255-6°C. (Found: C, 72.5; H, 4.7; N, 15.6. $C_{21}H_{16}N_4O$ requires C, 74.1; H, 4.7; N, 16.4%, $C_{21}H_{16}N_4O.(H_2O)_{1/2}$ requires C, 72.2; H, 4.9; N, 16.0 %). The analysis suggested either the presence of a half molecule of water of crystallisation, or the presence of some acyclic compound of type (VIII). The UV-spectrum showed no trace of acyclic compound, being that of a typical 1,2,4-triazole. (λ_{max}=268 mμ ; log ε_{max}=3.97).

(Xj): The reduction of the amide (Xe):

1g (Xe) was refluxed with $LiAlH_4$ (0.25g) in ether (50 ml) for 5 hours, stood at room temperature overnight, and aqueous methanol was added. Filtration, and evaporation of the filtrate gave 0.7g crude powder. Fractional recrystallisation from ethanol gave unchanged (Xe) (0.2g), and 0.3g. (Xj), as white crystals m.p. 151-2° C. (Found: C, 77.6; H, 5.7; N, 17.2. $C_{21}H_{18}N_4$ requires C, 77.3; H, 5.6; N, 17.2%)

This secondary amine thus appears to be a normal 1,2,4-triazole.

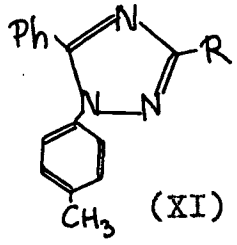
The ester (Xb) did not react with aniline or N-methylaniline on refluxing in ethanol for 10-12 hours. Nor was there any reaction between the azlactone (VIIa) and N-methylaniline to give a tertiary amide. There appeared to be some reaction between (VIIa) and phenylhydrazine, but a pure product could not be isolated.

The preparation of the acylsemicarbazone (Xg)

To (VIIa), suspended in methanol containing 10% water, was added excess semicarbazide.HCl. The mixture was just neutralised with sodium bicarbonate, and refluxed for 30 minutes. Concentration, dilution and cooling gave white crystals, recrystallised from aqueous ethanol as white prisms (Xg), m.p. 198-200° C. (slight decomp.) (Found: C, 59.1; H, 4.6, N, 25.6; $C_{16}H_{14}N_6O_2$ requires C, 59.6; H, 4.4; N, 26.1%)

The same compound was formed by treating a 10% solution of the triazole hydrazide (Xc) in glacial acetic acid, with a slight excess of aqueous sodium cyanate; thus confirming the structure as (Xg). A mixed m.p. of this product, made by the two different routes, was not depressed.

3) Rearrangements undergone by 2-phenyl-4-p-tolylazo-oxazolin-5-one (VIId) to give products of the type:



(XI)

a. R= -COOH
b. R= $-COOCH_3$
c. R= $-CONHNH_2$
d. R= $-CONH_2$

1-p-tolyl-5-phenyl-1,2,4-triazole-3-carboxylic acid (XIa) and its methylester (XIb).

Treatment of (VIId) suspended in methanol with excess aqueous KOH, heating the alkaline solution for 5 minutes, concentration, cooling, and cautious acidification with conc. HCl gave (XIa), as fine white needles from chloroform/petrol ether; m.p. 177-8° C (decomp.) (Found: C,68.3; H,4.7; N,14.9. $C_{16}H_{13}N_3O_2$ requires C,68.8; H,4.7; N,15.1%).

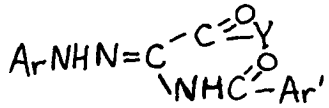
Rearrangement of VIId in methanol, made only faintly alkaline with aqueous KOH, Na_2CO_3 or $NaHCO_3$, and gentle heating for 5-15 minutes, when all the orange color had discharged ; gave on cooling, the ester (XIb). This recrystallised from benzene/petrol ether as short, white needles, m.p. 132-3° C. (Found: C,69.6, H,5.1; N,14.3. $C_{17}H_{15}N_3O_2$ requires C,69.6; H,5.1; N,14.3%).

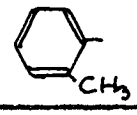
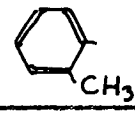
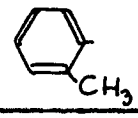
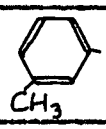
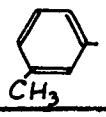
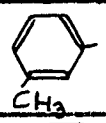
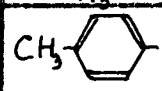
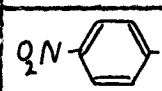
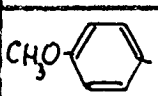
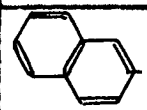
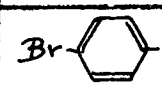
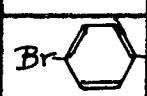
As in the previous case, under conditions of intermediate alkalinity the product was generally a mixture of the acid and the ester; the proportion of the latter decreasing at increasing pH.

The rearrangement of (VIId) with hydrazine.

Treatment of (VIId), suspended in methanol, with excess 85% hydrazine hydrate in the cold, gave at once a yellow precipitate, with discharge of the original deep orange color. Rapid recrystallisation from chloroform/petrol ether gave bright yellow

TABLE II **Intermediates formed during synthesis of 1,5-diaryl-3-substituted-1,2,4-triazoles**



Reference number	-Y	Ar-	Ar'-	m.p.°C. all with slight decomp.	Form and Colour
VIIb$_1$	-OCH$_3$		Ph-	136-8	yellow plates or flat needles
VIIb$_2$	-NHNH$_2$		Ph-	180-4	yellow powder
VIIb$_3$	-NH$_2$		Ph-	184-9	yellow powder
VIIc$_1$	-OCH$_3$		Ph-	181-4	pale yellow felted needles
VIIc$_2$	-NHNH$_2$		Ph-	191-3	pale yellow felted needles
VIIc$_3$	-NH$_2$		Ph-	166-8	orange powder
VIId$_1$	-NHNH$_2$		Ph-	157-9	yellow plates
VIIe$_1$	-NHNH$_2$		Ph-	170-6	yellow powder
VIIf$_1$	-NHNH$_2$		Ph-	158-162	yellow needles
VIIg$_1$	-NHNH$_2$		Ph-	168-171	yellow-brown powder
VIIh$_1$	-NHNH$_2$		Ph-	175-180	buff-yellow powder
VIIj$_1$	-NHNH$_2$	Ph-		158-160	yellow powder

plates, m.p. 156-160° C., with vigorous decomposition. Further recrystallisation depressed the m.p., and increased the melting range, e.g. after three recrystallisations part melted at 148-150° C, and most of the residue at 157-9° C (decomp.). The initial product, which could thus not be purified, was presumably an acyclic intermediate (VIId$_1$; Table II).

Heating (VIId$_1$) for 2-3 minutes with 2 N aqueous sodium carbonate in methanol (5vol.), gave rapid solution, and discharge of the yellow color. On cooling buff crystals precipitated, which after charcoaling and recrystallisation from chloroform/petrol ether formed white prisms (XI c), m.p. 149-150.5° C. (Found: C, 65.5; H, 4.9; N, 23.6. $C_{16}H_{15}N_5O$ requires C, 65.5; H, 5.1; N, 23.9%).

Alternatively: 2.2 g (VIId) suspended in methanol (50 ml) was treated with a slight excess of 85% hydrazine hydrate in the cold. After 5 minutes water (10 ml.) and 2N NaOH solution (1-2 ml.) were added, and the mixture heated gently for 2-3 minutes. Filtration, concentration and cooling gave (XIc) directly (1.9 g). The spectra of the cyclic and acyclic hydrazides are described in Section E.

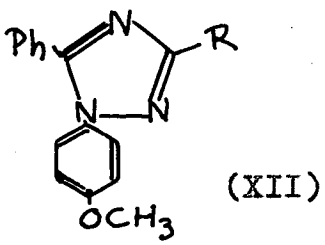
0.3 g of the ester (XIb) refluxed in ethanol (10 ml.) for 1 hour, with 85% hydrazine hydrate (2 ml.) gave, on concentration and dilution, 0.25 g. (XI c), m.p. 149-150° C, identical with the cyclised product from the reaction between (VIId) and hydrazine hydrate.

The reaction between (VIId) and ammonia.

To 0.5 g. (VIId) suspended in 20 ml. methanol, was added 10 ml. conc. aqueous ammonia, and the mixture heated for 5 minutes until the orange color had disappeared, leaving a pale yellow solution. Much of the methanol was evaporated off, the pH adjusted to about 8, with conc. HCl, and the solution extracted with chloroform. On acidification of the residual aqueous solution a few mg of the triazole acid (XI a) were obtained.

The chloroform extract was evaporated to dryness, and the residual crude powder, containing some tar, was recrystallised three times from benzene/petrol ether, as shimmering, white plates (0.17g; presumably XId), m.p. 155-6°C. (Found: C, 70.8; H, 5.2; N, 18.8. $C_{16}H_{14}N_4O \cdot {}^1/_3 (C_6H_6)$ requires C, 71.0; H, 5.3; N, 18.4%). The analysis does not prove the structure, but suggests that some benzene is still tightly bound in the molecule.

4) Rearrangements undergone by 2-phenyl-4-p-methoxy-phenylazo-oxazolin-5-one (VIIf), to give compounds of the type:



(XII)

a. R= -COOH
b. R= $-COOCH_3$
c. R= $-CONHNH_2$
d. R= $-CONH_2$

1-p-methoxy-phenyl-5-phenyl-1,2,4-triazole-3-carboxylic acid (XIIa) and its methylester (XIIb).

To crude (VIIf), suspended in methanol, was added 20% aqueous KOH until the mixture was strongly alkaline. Gentle heating for 2-3 minutes discharged the deep red color. Concentration, dilution with water, and careful acidification with conc. HCl gave the crude acid (XIIa). This was purified by solution in aqueous $NaHCO_3$, and reprecipitation with hydrochloric acid; followed by charcoaling and recrystallisation from chloroform/petrol ether, as white crystals, m.p. 176-7°C (decomp.). (Found: C, 65.0; H, 4.6; N, 13.8. $C_{16}H_{13}N_3O_3$ requires C, 65.1; H, 4.4; N, 14.2%).

To crude (VIIf) in methanol, as before, was added aqueous KOH, or preferably aqueous Na_2CO_3, until pH 7-9, and the mixture was then heated gently until the red color had disappeared (10-30 minutes). On dilution a soft, orange tarry precipitate was obtained, which was washed with aqueous $NaHCO_3$, and then charcoaled and recrystallized from benzene/petrol ether. After drying in vacuo over silica (XIIb) was obtained as fine white needles, m.p. 106-7°C. (Found: C, 65.9; H, 4.8; N, 13.5 . $C_{17}H_{15}N_3O_3$ requires C, 66.0; H, 4.9; N, 13.6%). Small amounts of the acid (XIIa) were usually formed together with the ester, even when great care was taken.

Reaction of (VIIf) with ammonia solution:

To crude (VIIf) suspended in methanol was added excess conc. ammonia solution. There was immediate partial discharge of the original deep red color, completed on gentle heating for 15 mins, as all went into solution. Neutralisation with HCl, and dilution with water, gave a heavy cream precipitate, which was filtered off and washed with water. Recrystallisation from chloroform/petrol ether gave fine, white needles (XIId) m.p. 183-4°C. (Found: C, 65.2; H, 4.7; N, 18.4. $C_{16}H_{14}N_4O_2$ requires C, 65.8; H, 4.7, N, 18.8%). There was no indication of any stable acyclic intermediate, or solvent of crystallisation.

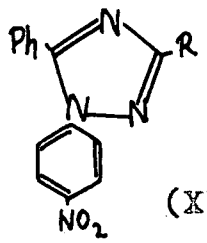
Reaction of (VIIf) with hydrazine hydrate:

resembled that of (VIId). (VIIf), suspended in methanol, and treated with excess 85% hydrazine hydrate in the cold, gave at once a mass of yellow needles assumed (VIIf, Table II), which were filtered off after 5 minutes, and had m.p. 163-7°C (decomp.). Heating this intermediate for 3-4 minutes in aqueous methanol containing a few ml. 2N Na_2CO_3 caused discharge of the yellow

color, as all went into a clear solution. The crystals which precipitated on cooling were charcoaled and recrystallised from chloroform/petrol ether, as white needles or prisms m.p. 165-7° C (XIIc). (Found: C, 61.8; H, 5.0; N, 22.3. $C_{16}H_{15}N_5O_2$ requires 62.6%C; H, 4.8; N, 22.4%). It was not necessary to isolate ($VIIf_1$) before the treatment with Na_2CO_3.

(XIIb) (3.3 g) were refluxed 30 minutes with 85% hydrazine hydrate (3 ml) in methanol (30 ml). On neutralisation and dilution 2.9 g crystals were obtained, m.p. 164-6° C, identical with (XIIc) but not with ($VIIf_1$). A mixed m.p. of (XIIc) and ($VIIf_1$) was depressed.

5) Rearrangements undergone by 2-phenyl-4-p-nitro-phenylazo-oxazolin-5-one (VIIe) to compounds of a type:



(XIII)

a. R= -COOH
b. R= $-COOCH_3$
c. R= $-CONHNH_2$

1-p-nitro-phenyl-5-phenyl-1,2,4-triazole-3-carboxylic acid methylester (XIIIb).

To crude (VIIe) suspended in methanol, was added sufficient aqueous 20% KOH to make the mixture just alkaline, and all was boiled gently for 30 minutes. The tarry precipitate, which formed on dilution gave no extract with aqueous Na_2CO_3. Charcoaling and recrystallisation four times from chloroform/petrol ether or benzene/petrol ether gave cream needles, m.p. 179-181° C (XIIIb) (Found: C, 59.7; H, 4.0; N, 17.2%; $C_{16}H_{12}N_4O_4$ requires C, 59.7; H, 3.7; N, 17.1%).

Treatment of (VIIe) with more concentrated alkali, in an attempt to form the acid (XIIIa) gave a mixture of the ester (XIIIb) and a trace of crude acid, m.p. 170-180° C. (decomp.), which seemed to decarboxylate readily, on attempted purification.

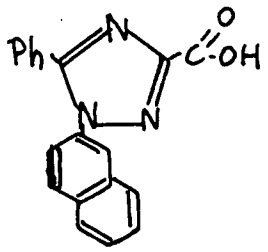
Reaction of (VIIe) with hydrazine hydrate:

Crude (VIIe) suspended in methanol, and treated with a slight excess of 85% hydrazine hydrate, gave a red tarry precipitate, after gentle heating for 5 minutes. The red color discharged on neutralisation with dilute HCl; and after charcoaling and recrystallisation from chloroform/petrol ether the product, presumably ($VIIe_1$), was obtained as a yellow-brown powder, m.p. 170-6° C (decomp.). 2 g of this compound were suspended in 50% ethanol (40 ml), 2 N Na_2CO_3 (3 ml) were added, and the mixture heated gently for 5 minutes, as all dissolved, giving a deep red solution. On neutralisation and dilution a yellow powder precipitated (1.7 g). This was charcoaled and recrystallised five times from chloroform/petrol ether, as a buff powder (XIIIc), m.p. 201-3° C. (Found: C, 55.3; H, 4.1; N, 25.7. $C_{15}H_{12}N_6O_3$ requires C, 55.5; H, 3.7; N, 25.9%).

On one occasion, when a small amount of (VIIe) was suspended in a very large excess of methanol, and all boiled for some time with an excess of hydrazine hydrate, the triazole (XIIIc) was obtained directly. (XIIIc) was also formed readily by refluxing (XIIIb) with excess hydrazine hydrate in ethanol for 15 minutes. The product was identical with the cyclised product from the rearrangement.

The nitro group appeared to effect the reactions adversely; much tar was obtained throughout, and products were difficult to isolate and purify.

6) Rearrangements undergone by 2-phenyl-4-(2-naphthylazo)-oxazolin-5-one (VIIg) to give products of a type:



(XIV)

1-(2-naphthyl)-5-phenyl-1,2,4-triazole-3-carboxylic acid (XIV).

Crude (VIIg) was suspended in methanol (5-8 vol.), and 20% KOH was added dropwise, with gentle heating, keeping the solution just alkaline to litmus. Reaction was difficult, considerable amounts of brightly coloured tars being formed, and even with the greatest care no 1,2,4-triazole-carboxylic acid ester could be isolated. On careful acidification, extraction of the precipitated tars with aqueous $NaHCO_3$, and reprecipitation with dilute HCl, small amounts of the acid (XIV) only, were obtained. This formed long needles from chloroform/petrol ether, or from methanol; m.p. 193-4° C (decomp.). (Found: C, 71.8, H, 4.2; N, 13.3. $C_{19}H_{13}N_3O_2$ requires C, 72.3; H, 4.2; N, 13.3%).

Reaction of (VIIg) with hydrazine hydrate.

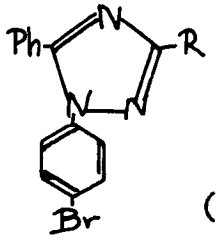
Crude (VIIg) suspended in methanol, reacted readily with excess 85% hydrazine hydrate in the cold, or on heating for 2-3 minutes. The red color discharged rapidly, and on cooling a buff powder precipitated, m.p. 168-171° C (slight decomp.), which was only very slightly soluble in organic solvents. This decomposed vigorously on further heating, and appeared to be the acyclic hydrazide (VIIg). It did not undergo the Kalb-Gross alkaline oxidation with $K_3Fe(CN)_6$, no aldehydes being detected. It was not found possible to ring close (VIIg) to

the triazole acid hydrazide. Treatment with dilute solutions of Na_2CO_3 or NaOH in aqueous ethanol, gave only crude tarry breakdown products.

Due to deactivation and/or steric hindrance the β-naphthyl group interfered with the azlactone conversions to triazoles.

As the products were so unsatisfactory the triazoles containing the -2-naphthyl-group were not further investigated.

7) Rearrangements undergone by 2-phenyl-4-p-bromo-phenylazo-oxazolin-5-one (VIIh) to give products of the type:



(XV)

a. R= -COOH
b. R= $-COOCH_3$
c. R= $-CONHNH_2$
d. R= $-CONH_2$

1-p-bromo-phenyl-5-phenyl-1,2,4-triazole-3-carboxylic acid (XVa) and its methyl ester (XVb).

Crude (VIIh) was suspended in 5-8 vol. of methanol, and 20%KOH was added until the mixture was faintly alkaline to litmus. After boiling until all orange azlactone had reacted (15 mins.), water was added and the crude product filtered off. After washing with aqueous $NaHCO_3$, this was charcoaled, and recrystallised three times from chloroform/petrol ether, to give (XVb), as colorless, rectangular prisms., m.p. 138-9° C., after drying over silica in vacuo. (Found: C, 55.9; H, 3.5; N, 10.4; Br. 22.8. $C_{16}H_{12}N_3O_2Br$ requires C, 54.2; H, 3.4; N, 11.6; Br, 22.1%).

When excess KOH was added to a suspension of (VIIh) in methanol the only product was the triazole acid (XVa), charcoaled and recrystallised three times from benzene/petrol ether, as white crystals, m.p. 179-180° C. (decomp..) (Found: C, 52.2; H, 3.0; N, 10.7; $C_{15}H_{10}N_3O_2Br$ requires C, 52.3; H, 2.9; N, 12.2%).

Preparation of the hydrazide (XVc).

2o (VIIa),suspended in methanol,was added a slight excess of 85% hydrazine hydrate,and all heated gently for 2-3 minutes, by which time all the azlactone had reacted.The pale yellow, fine,felted needles,m.p.175-180°C.(decomp.) were presumably the acyclic intermediate ($VIIa_1$).This cyclised readily by the usualtreatment with dilute aqueous Na_2CO_3 in ethanol,all going into solution on heating for 2-3 minutes.On cooling,cream crystals precipitated.These were charcoaled and recrystallised four times from chloroform/petrol ether,as white prisms,m.p. 175-7°C(XVc) . (Found:C,50.2;H,3.4;N,19.4. $C_{15}H_{12}N_5OBr$ requires C,50.3;H,3.4;N,19.5%).

Crystals identical with (XVc) were formed in near quantitative yield when the triazole ester (XVb) was refluxed in ethanol for 2o minutes,with a slight excess of 85% hydrazine hydrate. A mixed m.p. of (XVc) and ($VII a_1$) was depressed.

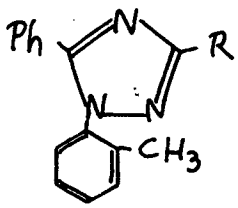
Preparation of the amide (XVd).

(VIIa) was suspended in methanol,excess conc. aqueous ammonia added,and the mixture heated for 5 minutes, to complete the rapid reaction.Neutralisation and cooling gave buff precipitate which was charcoaled and recrystallised several times from chloroform/petrol ether,as white crystals (XVd),m.p. 176.5-178°C. (Found:C,52.0;H,3.0;N,14.6.* $C_{15}H_{11}N_4OBr$ requires C,52.5;H,3.2; N,16.3%).

Note: In connection with analytical figures marked with an asterix,reference should be made to Appendix (A): 'Nitrogen analyses in the 1,2,4-triazole series.'

In the previous subsections (3,4,5,7) the resultant 1,2,4-triazoles have all been on the type '1-para-substituted-5-phenyl-', and there was some indicationthat the varying substituent had some effect on the ease and course of the rearrangement. To compare any effect of variation in the position of the radicals the series was extended to include the 1-ortho-tolyl-5-phenyl-(8); 1-meta-tolyl-5-phenyl-(9); and 1-phenyl-5-p-bromo-phenyl-1,2,4-triazoles (10).

8) Rearrangements undergone by 4-o-tolylazo-2-phenyl-oxazolin-5-one (VIIb) to compounds of the type:



(XVI)

a. R= -COOH
b. R= $-COOCH_3$
c. R= $-CONHNH_2$
d. R= $-CONH_2$

Reaction of (VIIb) with methanol/KOH.

Crude (VIIb) was suspended in methanol and aqueous KOH added to pH 7-9, as before; the mixture was heated gently for 1o mins. to complete the discharge of the orange color. On concentration, dilution with water, and cooling a felted mass of pale, creamy-yellow needles precipitated. These gave a deep yellow chloroform or benzene solution. Charcoaling and recrystallisation from chloroform/petrol other gave pale yellow needles, m.p. 137-9° C. (slight decomp.). There was vigorous decomposition on further heating. (Found: C,66.2; H,5.6; N,13.5 . $C_{17}H_{17}N_3O_3$ requires C,65.6; H,5.5; N,13.5%). This analysis indicated that the product was almost entirely the acyclic ester (VIIb$_1$; Table II), a conclusion which was supported by a UV spectrum not typical of 1,2,4-triazoles (λ_{max} =23o, 29o, 336 mμ ; logε_{max} =4.22; 3.82; 4.o1.)

On one occasion only, on standing the neutral mother liquors, after removal of the precipitated acyclic ester, for two days at room temperature, a small amount of white precipitate formed. This was recrystallised from benzene / petrol ether as fine white needles (XVIb), m.p. 92-4° C, (Found: C, 69.65; H, 5.2; N, 14.3. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.2; N, 14.3%).

The UV spectrum indicated this was a normal triazole. (λ_{max}=237 mμ ; Log ε_{max}=4.01). This preparation was not reproducible, as subsequent results indicated that the rate of hydrolysis of the ester group was comparable with the rate of ring closure of the acyclic ester, under even mildly basic conditions.

Careful attempts to cyclise (VIIb$_1$) to (XVIb), by gentle heating in aqueous methanol, with the addition of small amounts of $NaHCO_3$ or Na_2CO_3, failed. In these cases the only product was the triazole acid (XVIa), identical with that formed directly when (VIIb) was treated with excess KOH in aqueous methanol. (XVIa) was charcoaled and recrystallised from chloroform/petrol ether as white crystals, m.p. 171-2° C. (decomp.). (Found: C, 67.9; H, 4.7; N, 14.9 . $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.1%).

In all cases where (VIIb) was treated with excess alkali there was a strong smell of o-cresol, suggesting that some of the azlactone hydrolysed instead of rearranging.

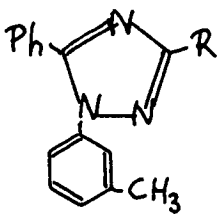
Reaction of (VIIb) with hydrazine hydrate in methanol in the usual manner, gave, initially, the expected intermediate (VIIb$_2$), as a bright yellow powder, m.p. 180-4° C. (decomp.). Treatment with dilute aqueous Na_2CO_3 in methanol caused most to cyclise within 5 minutes; but some yellow color remained; and there also seemed to be some decomposition of the acyclic compound. The triazole acid hydrazide (XVIc) recrystallised from benzene/ petrol ether, as cream prisms, m.p. 152-3° C. (Found: C, 65.9; H, 5.3; N, 23.6. $C_{16}H_{15}N_5O$ requires C, 65.5; H, 5.3; N, 23.9%).

Only a very slight trace of (XVIc) formed when (VIIb$_1$) was

reacted with hydrazine hydrate in methanol, the main part decomposing to a tar.

A yellow intermediate (VIIb$_3$), m.p. 184-9°C. (decomp.), similar to (VIIb$_2$), was formed when (VIIb) was reacted with aqueous NH_3 in methanol. Treatment with aqueous Na_2CO_3 in methanol readily gave white crystals from benzene/petrol ether, m.p, 180-3°C, presumably (XVId). Few were available, and the compound was not further characterised.

9) Rearrangements undergone by 2-phenyl-4-m-tolylazo-oxazolin-5-one (VIIc) to products of a type:



(XVII)

a. R= -COOH
b. R= -COOCH$_3$
c. R= -CO.NHNH$_2$

Reaction of (VIIc) with methanolic KOH, as for (VIIb), in near neutral suspension, gave creamy-yellow felted needles, m.p. 181-4°C. (slight decomp.), presumably (VIIc$_1$). They gave deep yellow chloroform or benzene solutions. The acyclic structure was supported by a UV spectrum not typical of triazoles (λ_{max}=230, 290; 332mμ ; log ϵ_{max}=4.18; 3.77; 4.20). After four recrystallisations of (VIIc$_1$) from chloroform/petrol ether, most melted at 165-9°C., probably due to slow partial cyclisation to (XVIIb).

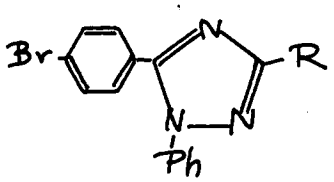
(VIIc$_1$) with dilute aqueous Na_2CO_3 in methanol was usually converted directly to the triazole acid (XVIIa), identical with that formed when (VIIc) reacted directly with excess KOH/methanol. (XVIIa) recrystallised from chloroform/petrol ether as white crystals, m.p. 182-3° C. (decomp.). (Found: C, 68.3; H, 4.7; N, 14.8. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.1%). However, on one occasion, when the reaction pH was only faintly alkaline, some of the

acid formed (XVIIa), was accompanied by a small amount of the triazole ester (XVIIb). This was charcoaled and recrystallised from chloroform/petrol ether as white rectangular prisms, m.p. 127-8°C. (Found: C, 70.2; H, 5.3; N, 14.4. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.2; N, 14.3%).

As with the preceding ortho-tolyl compounds the rate of hydrolysis of the ester, and the rate of cyclisation to the triazole seemed so similar, that this preparation was difficult to repeat. In both cases the acyclic esters (VIIb, and $VIIc_1$) could be reduced to the triazole alcohols (IIId and IIIc; Table III), by $LiAlH_4$ reduction. The UV spectrum was that of a normal 1,2,4-triazole (XVIIb) (λ_{max}=240 mμ; $\log \varepsilon_{max}$=4.04).

Reaction between (VIIc) and hydrazine hydrate, in methanol, at room temperature, gave a mass of pale yellow, felted needles, m.p. 191-3°C (slight decomp.), presumably ($VIIc_2$). All attempts to cyclise this acyclic compound, with dilute, aqueous Na_2CO_3 or $NaHCO_3$ in methanol, failed, and much tar appeared. Tars were also formed when ($VIIc_1$) was treated with hydrazine hydrate; and as very little (XVIIb) had been isolated, the desired acid hydrazide (XVIIc) was not obtained.

10) Rearrangements undergone by 2-p-bromo-phenyl-4-phenylazo-oxazolin-5-one (VII j) to compounds of the type:



(XVIII)

a. R= -COOH
b. R= $-COOCH_3$
c. R= $-CONHNH_2$

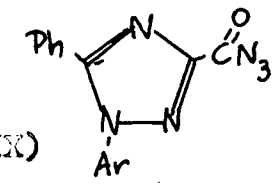
Reaction of (VIIj) with aqueous KOH in methanol, did not occur too readily; and it was necessary to make the mixture fairly alkaline to litmus and to boil for 10-30 minutes. The

crude product was charcoaled and recrystallised several times from benzene/petrol ether, as white rod-like needles, m.p. 157-9°C. (XVIIIb). (Found: C, 53.7; H, 3.6; N, 11.4. $C_{16}H_{12}N_3O_2Br$ requires C, 54.2; H, 3.4; N, 11.6%) The acid (XVIIIa) was not obtained pure, as it decarboxylated readily, with tar formation. The acid hydrazide (XVIIIc) formed readily on refluxing (XVIIIb) with excess 85% hydrazine hydrate in methanol, for 1o minutes. Charcoaling and recrystallisation from benzene/petrol ether gave a cream powder, m.p. 159-161°C. (Found: C, 51.2; H, 3.5; N, 18.6.* $C_{15}H_{12}N_5OBr$ requires C, 5o.3; H, 3.4; N, 19.5%) A purer compound could not be obtained. A mixed m.p. of (XVIIIb) and (XVIIIc) was strongly depressed.

Treatment of (VIIj) with excess 1oo% hydrazime hydrate in methanol, gave a rapid reaction in the cold, completed by warming for 2-3 minutes. The pale yellow product was rather insoluble in most organic solvents, but a small part recrystallised from its deep yellow chloroform solution as a pale yellow powder, m.p. 159-160°C. (decomp.), presumably (VIIj). A mixed m.p. of (VIIj) and (XVIIIc) was depressed.

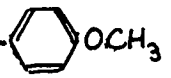
($VIIj_1$) could not be cyclised to (XVIIIc) by aqueous Na_2CO_3 or NaOH in methanol, only tars being formed. However, a trace of compound identical with (XVIIIc) was obtained by gentle heating with aqueous $NaHCO_3$/methanol, the main product still being a tar. In this case the rate of breakdown in alkali of the acyclic acid hydrazide, seemed comparable with the rate of cyclisation to the triazole .

11) 1,5-diaryl-1,2,4-triazolo-3-carboxylic acid azides (XIX).



(XIX)

a. Ar = -Ph

b. Ar = 

One 1,2,4-triazolo acid azide has been previously reported (75), viz. 1-p-nitro-phenyl-5-hydroxy-1,2,4-triazolo-3carboxylic acid azide. This was stated not to undergo the Curtius rearrangement.

1,5-dimesityl-1,2,4-triazolo-3-carboxylic acid azide (XIIIc)

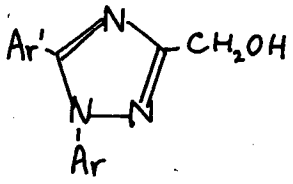
To a solution of the triazolo acid hydrazide (XIc, 4.7g) in glacial acetic acid (50 ml) and 2N aqueous hydrochloric acid (15 ml), at 0-5° C, was added a solution of sodium nitrite (1.5g) in water (15 ml). After 5 minutes the mixture was further diluted with water, and the heavy white precipitate was filtered off and washed with water. Recrystallisation from aqueous methanol and drying at 60° C in vacuo gave (XIIIa, 4.5g, 92%) as fine white needles, m.p. 124-5° C. (vigorous decomp.). (Found: C, 62.1; H, 5.7; N, 20.4. $C_{15}H_{16}N_6O$ requires C, 62.1; H, 5.5; N, 28.9%).

(XIIc) treated with sodium nitrite, as above, gave (XIIIb) in near theoretical yield, as white powder from benzene/petrol ether; m.p. 107-8°C (vigorous decomp.). (Found: C, 60.5; H, 4.0; N, 25.9. $C_{16}H_{12}N_6O_2$ requires C, 60.0; H, 3.8; N, 26.2%).

Both compounds gave a positive test for acid azides when treated with aqueous NaOH, followed by $HNO_3/AgNO_3$. The properties of the acid azides were not investigated to any extent. They were, however, stable up to their melting points, the decomposition products smelling of isocyanates (R.CO), suggesting that some rearrangement had occured. (XIIIa) did not decompose on boiling for short periods in dry benzene, or toluene, but did so in xylene. It was cleaved readily by boiling for a few seconds

in dilute NaOH, to give the parent acid (Xa). There was no detected reduction of (XIX) with Raney nickel and diethylamine in methanol, kept overnight at room temperature under one atmosphere of hydrogen. The azide was largely converted to the triazole ester (Xb), under these conditions. However, (XIXa) was unchanged by short periods of boiling in methanol, or by standing overnight with methanol and Raney nickel alone.

12) 1,5-diaryl-3-hydroxymethyl-1,2,4-triazoles of the type:

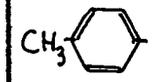
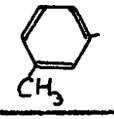
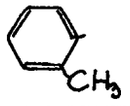
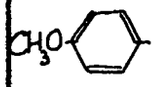
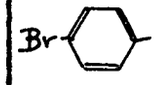
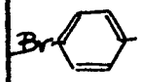


(III) (Table III)

Two hydroxymethyl-1,2,4-triazoles have been previously described (40), viz. the parent compound, and the 1-benzyl-3-(or 5)-hydroxymethyl-1,2,4-triazole. Both were isolated as the hydrochlorides, and not pure in the free state. They were reported to form by the action of formalin in a sealed tube on the C-unsubstituted-1,2,4-triazole, in 30% and 60% yields respectively. The former alcohol was also prepared by a more devious route via the reduction of the difficultly prepared ethylester of 1,2,4-triazole-3-carboxylic acid, with $LiAlH_4$ in tetrahydrofuran.

The reaction between (I) and formalin, as described (40), was not found to be a practicable route. The only triazole definitely identified in the reaction mixture was unchanged (I), isolated as the free base, its hydrochloride, or its picrate. A small amount of a second, unidentified picrate was also obtained in the last case. (Section D, Ib, ix).

TABLE III 1,5-diaryl-3-hydroxymethyl-1,2,4-triazoles (III)

Reference number	Ar-	Ar^1-	Crystal form	m.p. °C.	Approx. yield %	Analyses: Found C	H	N%	Analyses: Theoretical C	H	N%
IIIaA	Ph-	Ph-	White prisms	132-3	65-80	71.8	5.6	16.0	$C_{15}H_{13}N_3O$ requires	71.7	5.2	16.7
IIIaB	Ph-	Ph-	Prisms	153-4		71.8	5.2	15.9	Ditto.			
IIIb		Ph-	Plates or needles	151.5-152.5	85	72.6	5.6	15.7	$C_{16}H_{15}N_3O$ requires	72.4	5.7	15.8
IIIc		Ph-	Plates or needles	159-161	70	72.9	5.8	15.3	Ditto.			
IIId		Ph-	Needle clusters	136-8	45	72.4	5.6	15.9	Ditto.			
IIIe		Ph-	Prisms	152-3	80	68.8	5.4	14.6	$C_{16}H_{15}N_3O_2$ requires	68.3	5.4	14.9
IIIf		Ph-	Plates	164-6	65	54.9	3.9	— Br 23.8	$C_{15}H_{12}N_3OBr$ requires	54.6	3.6	12.7 Br 24.2
IIIg	Ph-		Needles	133-5	55	54.8	3.8	12.2	Ditto.			

All were recrystallised from benzene/petrol ether.

A typical example of the reduction was the preparation of 1-p-tolyl-3-hydroxymethyl-5-phenyl-1,2,4-triazole (IIIb).

To 0.5 g $LiAlH_4$ (Fm.0.3 g) in dry ether (15 ml) was added a suspension of 1-p-tolyl-5-phenyl-1,2,4-triazole-3-carboxylic acid methylester (IIb;3.7 g) in ether (30 ml); and the mixture was refluxed on a water bath for 5 hours. 10% aqueous methanol (10 ml) was added, and boiling continued until excess $LiAlH_4$ had reacted (20-30 mins.). Inorganic material was filtered off and washed with methanol, and the combined filtrates evaporated to 15-20 ml. Careful dilution with water gave a precipitate of (IIb;3.0 g;86%), as white plates or prisms when recrystallised from benzene/petrol ether, m.p. 151.5-152.5°C. (For analysis see Table III).

In general the preparation of the other alcohols was similar, with results as indicated in Table III. Use of more than a two-fold excess of $LiAlH_4$, or reaction periods much longer than those indicated tended to reduce the yields. This may have been due to some attack of the reagent on the 1,2,4-triazole ring.

Attempted reduction of 1-p-nitro-phenyl-5-phenyl-1,2,4-triazole-3-methyl-carboxylate (XIIIb) with $LiAlH_4$ in ether, failed, due to the expected interference by the $-NO_2$ group. Both normal and inverse addition of the $LiAlH_4$, followed by refluxing for 6 hours, left most of the ester unchanged; the only product, otherwise, being a little deep red tar.

In the preparation of the alcohols containing bromine (IIIf and IIIg), inverse addition of only a slight excess of $LiAlH_4$ was used.

1-o-tolyl-3-hydroxymethyl-5-phenyl-1,2,4-triazole (IIId) was obtained directly by reduction of the acyclic ester (VIIb,) with $LiAlH_4$ in 46% yield, indicating that cyclisation had occurred under the conditions of the reaction. Bright yellow, orange and brown colors appeared during the refluxing period, which were not observed during the reduction of any triazole ester;

and more tars formed than with the other reductions.

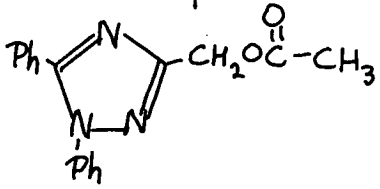
The isomeric 1-m-tolyl-5-phenyl-3-hydroxymethyl-1,2,4-triazole (IIIc) was formed by analogous reduction of the cyclised (XVIIb) or acyclic ester ($VIIc_1$) or mixtures of the two. When ($VIIc_1$) was present some yellow color appeared during the reaction. The yield was 70% in the first case, but as low as 50% when the acyclic ester was used.

In the first preparation of (IIIe) the initial product had a double m.p., 142-5°C, resolidifying and remelting 151-3° C. Heating this alcohol with dilute HCl, or recrystallising from benzene, gave a stable compound, m.p. 152-3°C. The UV spectrum of both was stable and identical (λ_{max}=226 mμ ; logε_{max}=4.26 shoulder at 256 mμ ; logε = 4.0).

The isomeric 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazoles (IIIaA and B).

Reduction of 1,5-diphenyl-1,2,4-triazole-3-methylcarboxylate (Xb) with $LiAlH_4$ in ether, gave rise to either a stable alcohol (IIIaB), m.p. 153-4°C, or a labile alcohol (IIIaA), m.p. 132-3°C. (Analyses Table III). A mixed m.p. of A and B was 131-150°C. Both alcohols were colorless.

(IIIaA) was readily converted to (IIIaB) by treatment, in solution, with dilute mineral acids, seeding with B, or standing at room temperature for several hours in methanol. Both were oxidised to the same acid (Xa) with chromic acid or alkaline $KMnO_4$; or to the same aldehyde (IV a) with $Pb(OAc)_4$. Treatment of (IIIaA or B) with acetyl chloride gave the same acetyl derivative ($IIIa_1$):



as white plates from benzene/petrol ether, m.p. 110-1°C.

(Found: C, 70.0; H, 5.2; N, 14.3. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.2 N, 14.3%).

In these last experiments it is probable that the labile A form was converted to the stable B form, before reaction occured. Thus they do not throw much light on the type of isomerism involved.

The UV absorption maximum of (IIIaA) at 261 mμ, changed to that of (IIIaB) at 248 mμ, in methanol solution. The spectra of these compounds are further discussed in Section E.

Section B.

Section B. 1,5-diaryl-1,2,4-triazole-3-aldehydes.

Discussion of the Syntheses.

As described in the introduction, 1,5-diaryl-1,2,4-triazole-3-aldehydes (IV), or their derivatives, have been successfully synthesised by two main routes:

(1a). The oxidation of the corresponding alcohols (III) with lead tetraacetate in benzene. This method proved the most satisfactory, and all the free aldehydes were isolated in this way. The advantage apparently lay in the use of a nonaqueous medium for the initial formation, and the nonreaction of the desired product with unchanged starting material.

(2a). The treatment of the 1,5-diaryl-1,2,4-triazole-carboxylic acid hydrazides (V) with potassium ferricyanide/aqueous ammonia, or other suitable alkaline oxidising agents (Kalb-Gross; 41). Most early work was done by this method, and many aldehyde derivatives were first obtained by its use. It was less suited than (1a) for isolation of the free aldehydes due to the tendency to condense with unchanged starting material.

In addition aldehyde derivatives were obtained, in a few cases, by two other methods:

(1b). The treatment of the alcohols (III) with N-bromo-succinimide, followed by hydrolysis of the product with conc. hydrochloric acid. This method seemed promising in the two cases tried, but was not used until after the free aldehydes had already been isolated. As the final, strongly acid, conditions would interfere with the isolation of the free product, there seemed no advantage over (1a).

(2b). The McFayden-Stevens reaction (49), or preferably its modification with powdered glass (54), gave rise to some aldehyde derivatives. The reaction was not suited to isolation of the free compounds, as the high reaction temperatures used encouraged very rapid condensation of the aldehydes with

other substances present. The routes followed are indicated in the diagram on page (13).

The isolation of the free aldehydes proved very difficult, until the exact reaction conditions were found. That they were present at the completion of the reaction periods was shown by their estimation by the normal oximation procedure (91). In the preparation of (IVa) by method (1a) a value of 46% free aldehyde was obtained; and by method (2a) 24 and 27%. Alternatively the aldehydes were estimated by rapid precipitation as derivatives, generally with 2,4-dinitro phenylhydrazine reagent (M), or occasionally as semicarbazones. When method (2a) was used with half quantities of oxidising agent the acylhydrazone, from condensation of (IV) with unchanged (V), formed in near quantitative yield. None of these derivatives isolated could be hydrolysed to the parent aldehyde.

The crude aldehydic products were finally purified by preparation of their Girard-T derivatives in aqueous solution, and extraction of non-aldehydic material. The aldehydes could not be satisfactorily regenerated by standard methods; the most promising being that of Teitelbaum (85), employing aqueous formaldehyde. Seven free aldehydes (IV) were obtained, by treatment of the aqueous solutions of their Girard-T derivatives with a mixture of formaldehyde and hydrochloric acid, in the presence of chloroform. The solvent ensured the removal of the product from the reaction mixture as soon as it formed. On evaporation of the chloroform extract the residual free aldehyde was usually readily obtained crystalline, by scratching in ether.

TABLE IV 1,5-diaryl-1,2,4-triazole-3-aldehydes (IV)

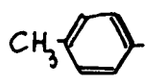
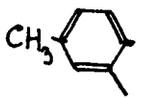
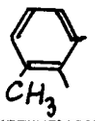
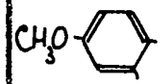
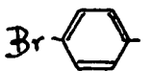
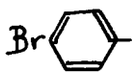
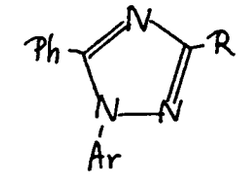
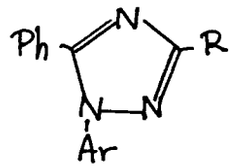
Reference Number	Ar-	Ar'-	m.p. °C.	Yield as free aldehyde	Yields as derivative %	Recrystallisation	Analyses: Found C	H	N%	Analyses: Theoretical C	H	N%
IVa	Ph	Ph-	144-5	50	Analysis as oxime: 46	Cream prisms from benzene/ petrol ether	72.5	4.7	16.6	$C_{15}H_{11}N_3O$ requires	72.3	4.5	16.8
IVb	 p.	Ph-	92-3	45	69 as semi-carbazone	"	73.2	5.3	16.1	$C_{16}H_{13}N_3O$ requires	73.0	5.0	16.0
IVc	 m.	Ph-	98-100	15	N deriv: 25 semi-carbazone: 18	"	72.8	5.0	15.8	Ditto			
IVd	 o.	Ph-	80-2	10	N deriv: 20	"	73.3	4.9	16.1	Ditto			
IVe		Ph-	93-4	40	N deriv: 35	"	68.7	4.7	14.5	$C_{16}H_{13}N_3O_2$ requires	68.8	4.7	14.1
IVf		Ph-	128-130	50	N deriv: 60 semi-carbazone: 46	"	55.4	3.2	12.1	$C_{15}H_{10}N_3OBr$ requires	54.9	3.1	12.8
IVg	Ph-		88-9	20	---	cream prisms from ether/ petrol ether	55.2	3.2	12.2	Ditto.			

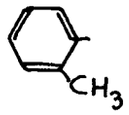
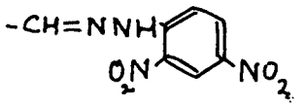
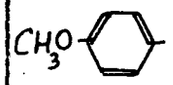
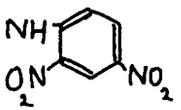
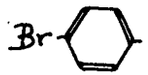
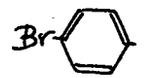
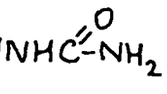
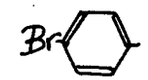
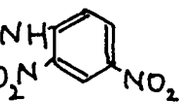
TABLE Va 1,5-diaryl-1,2,4-triazole-3-aldehyde derivatives



Reference number	Ar-	-R	m.p. °C.	Crystal formation	Analyses: Found C	H	N%	Analyses: Theoretical C	H	N%
IVa$_1$	Ph-	-CH=NOH	162-170	White prisms from chloroform/petrol ether	67.9	4.7	21.0	$C_{15}H_{12}N_4O$ requires	68.1	4.6	21.2
IVa$_2$	Ph-	-CH=NNHC(=O)NH$_2$	222-223	White needles from chloroform/ petrol ether	62.1	4.6	26.4*	$C_{16}H_{14}N_6O$ requires	62.7	4.6	27.4
IVa$_3$	Ph-	-CH=NNH-C$_6$H$_3$(NO$_2$)$_2$	247-249 (phase change? at 232)	orange-yellow powder from chloroform/ petrol/ether	58.2	3.6	22.2	$C_{21}H_{15}N_7O_4$ requires	58.7	3.5	22.8
IVa$_4$	Ph-	-CH=NNHC(=O)-C$_3$N$_2$Ph$_2$	232-3 and 247-9	white powder from aqueous ethanol	69.9	4.3	21.9	$C_{30}H_{22}N_8O$ requires	70.5	4.3	21.9
IVb$_1$	H$_3$C-C$_6$H$_4$-	-CH=NNHC(=O)NH$_2$	226-7	White crystals from aqueous ethanol	63.5	5.2	25.8	$C_{17}H_{16}N_6O$ requires	63.7	5.0	26.2
IVb$_2$	H$_3$C-C$_6$H$_4$-	-CH=NNH-C$_6$H$_3$(NO$_2$)$_2$	235-6	orange yellow powder from benzene/petrol ether	59.6	3.9	21.6	$C_{22}H_{17}N_7O_4$ requires	59.6	3.9	22.1

TABLE Vb 1,5-diaryl-1,2,4-triazole-3-aldehyde derivatives



Reference number	Ar-	-R	m.p. °C.	Crystal formation	Analyses: Found C	H	N%	Analyses: Theoretical C	H	N%
IVd$_1$			230-2 and 256-8	orange prisms from chloroform/ petrol ether	58.5	4.0	21.0	$C_{22}H_{17}N_7O_4 \cdot 1/2\ H_2O$ requires	58.4	4.0	21.7
IVe$_1$			227-8	yellow powder from benzene/ petrol ether	60.7	4.2	19.4	$C_{22}H_{17}N_7O_5 \cdot 1/2(C_6H_6)$ requires	60.3	4.1	19.7
IVf$_1$			173-5	white plates from chloroform/ petrol ether	52.9	3.4 Br 24.2	14.8*	$C_{15}H_{11}N_4OBr$ requires	52.5	3.2 Br 24.3	16.3
IVf$_2$			235-6	white crystals from chloroform/ petrol ether	49.6	3.5 Br 21.6	--	$C_{16}H_{13}N_6OBr$ requires	49.9	3.4 Br 20.8	--
IVf$_3$			223-4 or 252-4	orange-yellow powder from chloroform/ petrol ether	50.2	2.7	18.8	$C_{21}H_{14}N_7O_4Br$ requires	49.6	2.8	19.3

The properties of the 1,5-diaryl-1,2,4-triazole aldehydes (IV):

Considering the observed lability of these aldehydes (IV) in solution, in the presence of other compounds, and difficulty involved in their original isolation, they were unexpectedly stable when pure. All were unchanged after more than a year in stoppered sample tubes, and they showed no tendency towards aerial oxidation.

All were odorless, crystalline, odourless solids; but on melting they gave off pungent, choking fumes; those from a few milligrams being sufficient to affect a fairly large room. They were readily soluble in most organic solvents, least so in low boiling petrol ether; and insoluble in water and cold dilute mineral acids. All gave a silver mirror with Tollens' reagent and gave positive Schiff's tests; and none reduced Fehling's solution. Oxidation with H_2O_2 or $KMnO_4$ produced the corresponding carboxylic acid, and reduction with $LiAlH_4$ the corresponding alcohol.

Treatment with aqueous caustic alkali caused an apparently normal Cannizzaro reaction, as shown by the isolation of the respective acids. The corresponding alcohols, which should form simultaneously, were only isolated pure twice (IIIaß and IIIf), but non-acidic tarry material was always present. There was no reaction with aqueous Na_2CO_3 or $NaHCO_3$. No benzoin reaction with sodium cyanide could be detected. The aldehydes underwent the Perkin reaction, or, more satisfactorily, the Döbner reaction, to give the cinnamic acids (VI). Normal aldehyde derivatives, 2,4-dinitro phenylhydrazones, semicarbazones and oximes, formed.

In general the reactions of these compounds were those expected of normal aromatic aldehydes. In many ways they resembled those of N-substituted-1,2,3-triazole-C-aldehydes (35,93), or of similar aldehydes of the pyrazole (35), or imidazole (32) series. The presence of the N-aryl group prevented any interference by a nuclear -NH- (cf. Section C).

Experimental.

(Ia) Oxidation of 1,5-diaryl-3-hydroxymethyl-1,2,4-triazoles (III) with lead tetraacetate.

All oxidations were carried out in sodium dried benzene, and excess reagent decomposed with ethylene glycol. In most cases crude lead tetraacetate, containing some PbO_2, was used. This effectively "deactivated" reagent was generally more satisfactory than the much purer white material (Lights & Co), for which heating times had to be very carefully regulated. Too long heating destroyed nearly all the aldehyde. There was no detected oxidation with PbO_2 alone.

The crude lead tetraacetate used was synthesised from red lead/glacial acetic acid/acetic anhydride (Vogel: Textbook of Practical Organic Chemistry; third edition, page 199). The initial dark precipitate was kept in a vacuum desiccator over KOH, but was not recrystallised before use.

A representative experiment was as follows:

1-p-tolyl-5-phenyl-1,2,4-triazole-3-aldehyde (IVb)

1-p-tolyl-3-hydroxymethyl-5-phenyl-1,2,4-triazole (IIIb; 1.0 g.) and crude lead tetraacetate (2.5 g; slight excess) in sodium dried benzene (30 ml.), were refluxed for 6 hours. Excess reagent was decomposed by refluxing for 10-15 minutes more, after addition of a few drops of ethylene glycol. The mixture was filtered, and the benzene solution evaporated to near dryness. The residual syrup was dissolved at once in absolute ethanol (20 ml.) containing glacial acetic acid (1 ml.); Girard-T reagent (0.7 g.; slight excess) was added, and the mixture refluxed for 1 hour. Most of the ethanol was evaporated off; 50 ml water added, and sufficient $NaHCO_3$ to neutralise the acetic acid. Several extractions with chloroform removed non-aldehydic material. To the residual clear, aqueous solution (50 ml) was added 40% formalin (15 ml), conc. HCl (3 ml.) and chloroform (20 ml.),

and the mixture was heated gently for 3-5 minutes. Extraction was repeated once more with chloroform (2o ml), and the combined extracts were evaporated to dryness. The residual oil readily solidified on treatment with cold ether. Recrystallisation from benzene/petrol ether gave (IVb; o.42 g; 45%) as colorless prisms, m.p. 92-3° C. (Analysis, Table IV). The yield was 19%, isolated as the semicarbazone (IVb; Table Va) when reaction period was 3o minutes; and 69% with a reaction period of 6 hours.

Seven aldehydes were prepared by this method, with only minor modifications (Table IV). Yields of the purified aldehydes varied from 1o-5o%. Yields of up to 7o% were obtained by direct precipitation of derivatives from the initial crude reaction syrup. Most derivatives formed in greater yield by this means, than by method (2a).

When pure lead tetraacetate was used a heating period of 1 hour was sufficient, or even too long. With reaction periods of more than 3 hours only traces of aldehydes could be detected.

(Ib) Reaction of 1,2,4-triazole alcohols (III) with N-bromo-succinimide, followed by hydrolysis.

1,5-diphenyl-3-hydroxymethyl-1,2,4-triazole (IIIaB; o.6 g) and N-bromo-succinimide (o.6 g; 1:1, slight excess), in dry carbon tetrachloride (1o ml) and dry benzene (1o ml) were refluxed for 1.5 hours. The deep orange solution was cooled and filtered, and the filtrate was evaporated to dryness on a water bath. The residual acrid and lachrymatory syrup was boiled for 1o minutes with 2 N aqueous HCl (1o ml), and the mixture filtered hot. The filtrate was treated at once with 2,4-dinitro-phenylhydrazine reagent (N) in aqueous ethanol, to give a yellow precipitate. The undissolved residue from the initial treatment with aqueous HCl, was re-extracted twice in the same way, and (N) added to the filtrates. The combined yellow precipitates were recrystallised from chloroform and petrol ether to give yellow needles (IVa_3; o.3 g, 3o%), identical with those obtained by other three methods.

Similar treatment of (IIIf) with N-bromo-succinimide, followed by hydrolysis of the acrid, oily product with aqueous HCl, and reaction with (N), gave (IVf_3; 35%), as the higher melting form, m.p. 252-4°C. (IVf_3) obtained by precipitation with (N) from the crude reaction products from methods (1a) or (2a) always had m.p. 223-4°C. This lower melting form could be smoothly converted to the higher melting one by boiling for 5 minutes with conc. HCl and ethanol, and standing at room temperature for several hours. They are presumably cis/trans isomers. Although double melting points or apparent phase changes were noticed with several other aldehyde derivatives (IVa_3 ; IVa_4; IVd; Table V), this was the only case in which two stable forms were isolated.

(2a) The Kalb-Cross reaction on the 1,5-diaryl-1,2,4-triazole-3-carboxylic acid hydrazides (V).

The reagent found most satisfactory was $K_3Fe(CN)_6$/aqueous ammonia, in agreement with the original workers (41). The solvent used to dissolve the hydrazide had to be water miscible (ethanol); and sufficient had to be present in the aqueous solution to prevent precipitation when the hydrazide solution was added. This latter addition had to be as rapid as possible, but not too rapid to prevent the presence of unreacted hydrazide. About 10 ml. of aqueous ammonia was necessary per mole of reactant, and a large volume of liquid medium. If any of these precautions was neglected, or if a deficiency of the oxidising agent was used the formation of acylhydrazones was favoured. This tendency for the aldehydes formed to react with compounds present was so great that the desired aldehyde derivatives had to be precipitated from the reaction mixture immediately. A delay of only a few minutes reduced the yields considerably, giving instead crude mixtures of high melting by-products.

A typical reaction was the preparation of 1,5-diphenyl-1,2,4-triazole-3-aldehyde as its 2,4-dinitrophenylhydrazone (IVa_3).

1,5-diphenyl-1,2,4-triazole-3-carboxhydrazide (Xc; 2.0 g) in ethanol (30 ml) was added in a thin stream, with rapid stirring to a solution of $K_3Fe(CN)_6$ (4.8 g, 2 equivs.) in aqueous ethanol (4:1; 50 ml), containing 6% aqueous ammonia (20 ml); at room temperature. Immediately nitrogen evolution had ceased (1/2-1 minute) the mixture was just acidified with HCl, and a solution of 2,4-dinitrophenylhydrazine (0.6 g) in ethanol (20 ml) plus conc. HCl (1ml.), was added. After 20 minutes the yellow precipitate was filtered off, and recrystallised from chloroform/petrol ether as deep yellow needles (IVa ; 0.75 g; 24%), m.p. 247-9°C. (phase change 230-2°C), identical with those obtained by method 1a

A similar direct precipitation with semicarbazide gave 20% only of the semicarbazone, m.p. 222-3°C (IVa_2). An oxime and phenylhydrazone of the aldehyde (IVa) could not be obtained pure in this way. However, rapid estimation of the free aldehyde by oximation (91) gave values of 24% and 27% on successive runs. No pure oxime precipitated from these analytical soultions, but on one occasion fine white needles of the acylhydrazone (IVa_4), were isolated.

Similarly 2,4-dinitro phenylhydrazones (2) of the aldehydes were prepared from the following hydrazides((I) ;see Table V).

(1)	(2)	approx. yield
(XVIc)	(IVd_1)	20%
(XIc)	(IVb_2)	11%
(XIIc)	(IVe_1)	15%
(XVc)	(IVf_3)	18%.

No aldehyde could be detected on treatment of (XIIIc) by this method. Kalb and Gross state that no reaction occured in the presence of a nitro group (41).

Very small amounts of the free aldehydes could be isolated via the Girard-T derivatives, as described in (1a). As overall yields were seldom greater than 5% this route was less satisfactory.

Potassium metaperiodate has been recommended as oxidising agent for this type of reaction (94), but in this case it was found to favour acylhydrazone formation. With a deficiency of the reagent, and in the presence of an immiscible solvent the yields were nearly quantitative, as follows:

The preparation of (IVa_4; Table V).

A partial suspension of (Xc, 1.0 g.) in benzene (80 ml) was added to a solution of KIO_4 (1.2 g.) in 5% aqueous NH_3 (50 ml). The mixture was kept at 35-40°C, with occasional stirring,

until nitrogen evolution had ceased, and all suspended hydrazide had disappeared (2o minutes). The benzene solution was separated, charcoaled, and concentrated, to give (IVa_4; o.8 g) 88%. This formed as a white powder from aqueous ethanol; m.p. 252-3°C, to an opaque liquid, resolidifying and remelting 248-9°C to a clear yellow liquid. (Analysis, Table V).

Traces of (IVa_3) were obtained by treating the most benzene soluble tar with 2,4-dinitrophenylhydrazine reagent. This result showed that the aldehyde (IVa) had indeed formed, but most had rapidly condensed with excess acid hydrazide present.

(2b) <u>The McFadyen-Stevens Synthesis.</u>

Treatment of (Xh) with excess anhydrous potassium carbonate in glycerol or ethylene glycol, at 160°C, by the normal McFadyen-Stevens aldehyde synthesis (49), gave only traces of the aldehyde (IVa); isolated and identified by immediate precipitation as its derivative (IVa_3). Better results were obtained using theoretical amounts of alkali carbonate and powdered glass as catalyst (54). Yields of up to 43% (IVa_3) were obtained by rapid reaction with 2,4-dinitrophenylhydrazine reagent. In neither case could any free aldehyde be isolated by extraction procedures, as, with the ommission of immediate precipitation as a derivative, no aldehyde could be detected within a few minutes of completion of the reaction. This behaviour has been previously observed in the attempted synthesis of sensitive aldehydes by this reaction (25).

Due to high temperature, less easily removed solvents, and less readily available starting materials, this method was not preferred to the Kalb-Gross reaction, in which the free aldehyde did not react with other compounds present quite so rapidly. In most cases method (1a) was preferable to either.

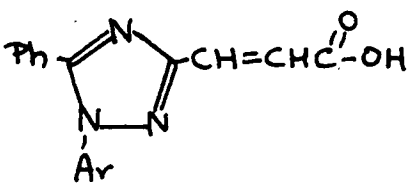
Preparation of (IVa_3) from (Xh):

1,5-diphenyl-1,2,4-triazole-3-benzene sulphonyl carboxhydrazide (Xh, 1.1 g) and powdered soft glass (o.6 g) in ethylene glycol (1o ml.), were heated to 16o-5°C, in an oil bath. To this was added anhydrous Na_2CO_3 (o.14 g; 1:1), with rapid stirring. $2^{1}/_{2}$ minutes after addition the vigorous nitrogen evolution had ceased, and the mixture was very rapidly cooled to room temperature. Ethanol (3o ml.) was added, followed at once by a solution of 2,4-dinitrophenylhydrazine (o.5 g.) in 5o% aqueous ethanol (1o ml.), containing a few drops of conc. HCl. After 2o minutes the yellow precipitate was filtered off, washed with water, and extracted with chloroform. Recrystallisation from chloroform/petrol ether gave (IVa_3; o.48 g, 43%) identical with that obtained by the previous methods. Even a slight delay in precipitating the derivative reduced the yield sharply.

Derivatives of the 1,5-diaryl-1,2,4-triazole-3-aldehydes are listed in (Table V). While the preparation and properties were on the whole, as expected, none of the oximes, semicarbazones, or 2,4-dinitrophenylhydrazones was successfully converted to the parent aldehyde. (IVa_3) was unaffected by treatment with p-nitrobenzaldehyde/2N HCl at 1oo° C for 6 hours; boiling with mineral acids; or attempted reaction with Girard-Preagent. (IVa_4) was not cleaved by mineral acids; and no free aldehyde could be detected on treatment of the oximes with nitrous acid. As described under method (1a) the Girard-T derivatives formed and cleaved normally.

A Döbner reaction on the free aldehydes gave the expected cinnamic acids :

1-p-tolyl-5-phenyl-3-(ß-acrylic acid) (XXb)



(XX)

a. Ar= -Ph
b. Ar=-p-tolyl
c. Ar=-p-anisyl

Crude, dry, 1-p-tolyl-5-phenyl-1,2,4-triazole-3-aldehyde (IVb; o.6 g.), and malonic acid (o.5 g.) in dry pyridine (15 ml), containing 3 drops of piperidine, were refluxed for 7 hours; until the very slow gas evolution had almost ceased. The solution was concentrated to 5 mls, poured into water (7o ml), and acidified with HCl. The crude precipitate was extracted with aqueous $NaHCO_3$, and the acid reprecipitated with HCl. Charcoaling and recrystallisation from benzene/petrol ether gave (XXb; o.18 g; 26%) as fine white needles, m.p. 2o3-4° C. (Found: C, 7o.8; H, 5.o; N, 13.3. $C_{18}H_{15}N_3O_2$ requires C, 7o.8; H, 5.o; N, 13.8%).

Similarly (XXa) was prepared in 33% yield from (IVa), recrystallising from benzene/petrol ether, as fine white needles, m.p. 2o1-2° C. (Found: C, 7o.4; H, 4.7; N, 14.4. $C_{17}H_{13}N_3O_2$ requires C, 7o.1; H, 4.5; N, 14.4%).

(XXc) was prepared in 18% yield from (IVe), as white crystals, m.p. 187-8° C. (Found: C, 67.3; H, 4.8; N, 12.6. $C_{18}H_{15}N_3O_3$ requires C, 67.3; H, 4.7; N, 13.1%).

A Perkin reaction on (IVa), with acetic anhydride/anhydrous sodium acetate gave small amounts of (XXa; 5%), identical with that obtained from the Döbner reaction.

Section C.

Section C.

The synthesis of some N-unsubstituted-1,2,4-triazole-C-aldehyde derivatives; and other N-unsubstituted-1,2,4-triazoles.

Discussion: The general reaction employed for the synthesis of these compounds was the condensation of imino-ethers with acylhydrazines to give 3,5-disubstituted-1,2,4-triazoles (Equation; pg. 15). In some cases cyclisation of intermediate amidrazones was necessary. The method has been used (64) to synthesise N-unsubstituted 1,2,4-triazoles with alkyl or aryl groups on the -C-atoms. The reaction has been extended to the synthesis of 1,2,4-triazoles containing a -C-acetal group, or other functional groups such as $-CH_2OCH_3$ or $-CH_2CN$.

In general the reaction proceeded readily in the case of imino-ethers with aryl, or alkyl-aryl substituents (e.g. XXIIb, c, d). Where R=$-CH_3$ condensation occured, but the products were often not easy to purify, and their exact structure was less easily determined. Due to the instability of formimino-methyl-ether (XXII; R=-H) it was not found possible to synthesise the corresponding 5-unsubstituted -1,2,4-triazoles, by this route.

All the acetals formed in this way were very stable to alkali, and were hydrolysed by strong acids. Aldehydes were liberated, as shown by the formation of 2,4-dinitrophenylhydrazones; but they seem to be very unstable, and have not yet been isolated in the free state.

Considerable differences in the properties of the N-substituted-1,2,4-triazole aldehydes, and the N-unsubstituted ones would be expected, due to the probable tautomerism previously mentioned (page 14). Such differences have, indeed, been noted in other N-heterocyclic series (32, 35).

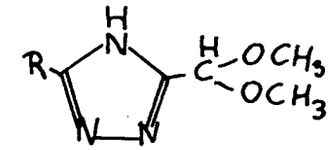
Methods used for the synthesis of N-substituted-1,2,4-triazole-C-aldehydes (Section B) were not, in general, useful for the synthesis of the N-unsubstituted ones. The N-unsubstituted-

1,2,4-triazole-3-carboxylic acids and their derivatives, though several have been described (40), are unstable or not readily accessible; and the Sawdey rearrangement (Section A) only gives rise to triazoles with a =N-N -aryl grouping.

No N-unsubstituted-1,2,4-triazole-C-acid hydrazides have been reported, thus preventing the ready use of the Kalb-Gross or McFadyen-Stevens reactions.

N-unsubstituted-1,2,4-triazoles form stable adducts with salts of heavy metals, more readily than do the N-substituted-triazoles. Oxidation with lead tetraacetate might thus not be as easy as with the N-aryl-triazoles. The presence of a free NH also introduces amphoteric properties which interfere with extraction from acidic or basic solution, and preclude previously used purification and isolation methods.

TABLE VIa **5-substituted-1,2,4-triazole-3-aldehyde dimethyl acetals.**



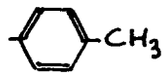
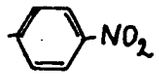
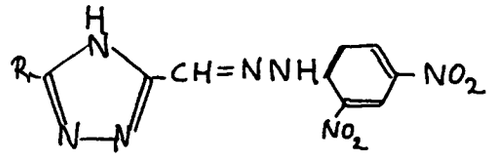
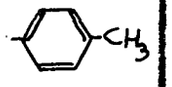
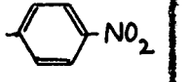
Reference number	R	m.p. °C.	Approx. yield %	Crystals	Analyses: Found C	H	N%	Analyses: Theoretical	C	H	N%
XXIIIa	$-CH_3$	96-101	50	White plates or needles from benzene/petrol ether	44.0	7.1	25.8	$C_6H_{10}N_3O_2 \cdot 1/2\,H_2O$ requires	43.4	7.3	25.3
XXIIIb	-Ph	102-3	60	Prismatic needles from benzene/petrol other	60.0	6.0	19.3	$C_{11}H_{13}N_3O_2$ requires	60.25	6.0	19.2
XXIIIc	$-CH_2Ph$	102-3	70	Plates from benzene/petrol ether	61.8	6.5	17.6	$C_{12}H_{15}N_3O_2$ requires	61.8	6.5	18.0
XXIIId		127-8	40	Plates from ether/petrol ether	62.2	6.5	17.6	Ditto			
XXIIIe		168-9	50	Pale yellow needles or plates from methanol/ether	47.2	5.1	20.0	$C_{11}H_{12}N_4O_4 \cdot H_2O$ requires	46.8	5.0	19.9

TABLE VIb. 5-substituted-1,2,4-triazole-3-aldehyde 2,4-dinitro-phenylhydrazones.



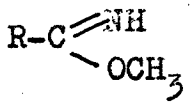
Reference number	R	m.p. °C. (slight decomp.)	Crystals	Analyses: Found C	H	N%	Analyses: Theoretical	C	H	N%
XXIIIa$_1$	$-CH_3$	254-6	yellow powder from aqueous methanol	40.7	3.4	31.9 O: 23.8	$C_{10}H_9N_7O_4 \cdot 1/2\ H_2O$ requires	40.0	3.4	32.6 O: 24.0
XXIIIb$_1$	-Ph	286-8	yellow needles from aqueous pyridine	51.3	3.3	27.3	$C_{15}H_{11}N_7O_4$ requires	51.0	3.1	27.75
XXIIIc$_1$	$-CH_2Ph$	243-5	yellow powder from aqueous pyridine	52.6	3.7	26.4	$C_{16}H_{13}N_7O_4$ requires	52.3	3.6	26.7
XXIIId$_1$		279-281	yellow needles from aqueous pyridine	56.5	4.1	25.1	$C_{16}H_{13}N_7O_4 \cdot C_6H_5N$ requires	56.2	4.2	25.6
XXIIIe$_1$		293-3	yellow plates from aqueous ethanol	43.3	3.2	(~26)	$C_{15}H_{10}N_8O_6 \cdot H_2O$ requires	43.3	3.0	26.9

Experimental .

(I) 5-substituted-1,2,4-triazole-3-aldehyde dimethyl acetals.

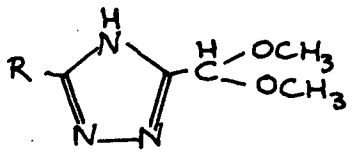
(XXI)

a. R= $-OCH_3$
b. R= $-NHNH_2$



(XXII)

a. R=$-CH_3$
b. R=$-Ph$
c. R=$-CH_2Ph$
d. R=p-tolyl
e. R=p-nitro-phenyl



(XXIII)

a. R=$-CH_3$
b. R=$-Ph$
c. R=$-CH_2Ph$
d. R=-p-tolyl
e. R=-p-nitro-phenyl

Dichloroacetic acid was converted to dimethoxy-methyl acetate (XXIa), by treatment with sodium methylate; and esterification of the unstable acid, with methanol/dry hydrogen chloride at room temperature (72). The final methanolic solution of the ester, after neutralisation with sodium methylate, and filtration from precipitated NaCl, was used directly for preparation of the acid hydrazide (XXIb). Preliminary distillation of the ester reduced the yield.

Dimethoxy-acethydrazide (XXIb).

The methanolic solution (120 ml) of dimethoxy methyl acetate (XXIa), derived from 0.2 m (26 g) dichloro-acetic acid, was cooled in an ice and salt bath, and 100% hydrazine hydrate (15g; excess) was added dropwise, with stirring. After 30 minutes at room temperature the solution was filtered, if necessary, and

the clear filtrate refluxed for 18 hours. The solvent was removed in vacuo, and the residue extracted with chloroform (4x3o ml). The combined extracts were concentrated, leaving a residual clear syrup, which, on cooling, set to a mass of coarse needles (XXIb), (9.4 g; 4o% calculated on dichloroacetic acid). Recrystallisation from benzene, and drying in vacuo over silica/paraffin chips gave (XXIIb) as white prisms, m.p. 73-75°C. (Found: C, 36.2; H, 7.4; N, 2o.9. $C_4H_{10}N_2O_3$ requires C, 35.8; H, 7.5; N, 2o.9 %).

The imino-ethers (XXII) were synthesised by standard methods, and isolated as the hydrochlorides. In most cases (XXIIa-d) a slight excess of dry hydrogen chloride was passed through an equimolecular mixture of the nitrile and methanol, in an excess of dry ether. For the preparation of (XXIIc.HCl) the dry HCl was passed into a solution of p-nitro-benzonitrile in excess dry methanol. Condensation of these imino-ethers with (XXIb) gave rise to the acetals listed in (Table VI). Also listed in (Table VI) are the derivatives which formed on hydrolysis of these acetals, and reaction with 2,4-dinitro-phenylhydrazine.

5-phenyl-1,2,4-triazole-3-aldehyde dimethyl acetal (XXIIb).
Benzimino-methylether hydrochloride (9o) (XXIIb.HCl; 3.4 g; $\frac{M}{50}$) was added to a cold solution of sodium hydroxide (0.8 g; $\frac{M}{30}$) in dry methanol (2o ml). The precipitated sodium chloride was filtered off rapidly, and the filtrate added at once to dimethoxy-acethydrazide (XXIb; 2.7 g., $\frac{M}{50}$). The mixture was refluxed gently for 4o minutes, and then carefully evaporated to dryness, leaving a thick syrup (4.1 g), which set to a hard glass. Chromatography on alumina in chloroform as solvent and eluent, gave (XXIIIb; 2.65 g, 6o%) as clusters of white needles from benzene/petrol-ether. After drying in vacuo over P_2O_5/silica the product had m.p. 1o2-3°C.
(XXIIIb) heated just to boiling in ethanol solution, containing a slight excess of 2,4-dinitro-phenylhydrazine and 1o-15% conc. HCl, was readily converted to (XXIIIb$_1$). The heavy yellow

precipitate was filtered off after 1-2 hours at room temperature, or better after standing overnight, charcoaled, and recrystallised from aqueous pyridine. (XXIIIb$_1$) was slightly soluble in dioxan, ethyl acetate and pyridine, and nearly insoluble in most other organic solvents. After drying overnight at 50°C over P_2O_5/silica (XXIIIb$_1$) was obtained as fine, yellow needles, m.p. 286-8°C (slight decomp.). This showed that the free 1,2,4-triazole-3-aldehyde must have been produced by acid hydrolysis of the acetal. (For analyses, see Table VIb).

Attempted reaction of (XXIIIb) with formylhydrazine in methanol/conc. HCl did not give any condensation product. N_2H_4.HCl, m.p. 90-1°C which precipitated, was the only compound isolated from the reaction mixture.

1-benzyl-1,2,4-triazole-3-aldehyde dimethyl acetal (XXIIIc)

(XXIIc.HCl) (90) was added to sodium hydroxide (1:1) in dry methanol, and the filtrate added immediately to one equivalent of (XXIb). After refluxing for one hour the solution was evaporated to dryness, and the residual syrup extracted several times with ether. The residue from the ethereal solution, after evaporation of the ether, was charcoaled and recrystallised from benzene/petrol-ether, and dried in vacuo over P_2O_5 at 40°C. 60% (XXIIIc) was thus prepared as white plates, m.p. 101-2°C. (Table VIa. (XXIIIc) was converted to (XXIIIc$_1$) by the method described in the previous experiment.

Rapid treatment of (XXIIIc) with methanol/conc. sulphuric acid, followed by addition of ether, precipitated shimmering, white plates, m.p. 122-3°C, and containing C, H, N, O, S. This product has not been definitely identified, but analysis supports the formula ($XXIIIc.H_2SO_4 \cdot 1/2\ H_2O$.)
(Found: C, 42.6; H, 5.2; N, 12.1. $C_{12}H_{18}N_3O_{6\frac{1}{2}}S$ requires C, 42.2; H, 5.3; N, 12.3%).

5-p-tolyl-and 5-p-nitrophenyl-1,2,4-triazole-3-aldehyde dimethyl acetals (XXIIId and e) were similarly synthesised from (XXIb) (XXIId or e) (31,89) respectively. Both gave the corresponding derivatives on treatment with (N)/ ethanol/HCl viz. ($XXIIId_1$; e_1). The latter formed slowly, and in rather poor yield. Solvent of crystallisation was present in the case of ($XXIIId_1$), as the analysis indicated the presence of 1 molecule of pyridine/ molecule of the triazole derivative. Water of crystallisation was present in (XXIIIe) and ($XXIIIe_1$).

In the analogous reaction, as above, of equivalent amounts of acetimino-methyl-ether (XXIIa) (73) and dimethoxyacethydrazide (XXIb), in methanol, the product crystallised as white needles from benzene/petrol ether. This compound seemed hygroscopic, and even with strong, drying over P_2O_5/silica in vacuo the sharpest m.p. obtained was 96-101°C. The structure was not proved, but the properties resembled those of the previously described triazole acetals, and analysis suggested (XXIIIa. 1/2 H_2O) (Table VI).

Reaction of this acetal with (N) in ethanol/HCl at room temperature overnight, gave a yellow powder from aqueous methanol, m.p. 254-6°C. Here, again, the analysis suggested the presence of tightly bound water, though this is seldom observed with this type of derivative.

Both in this case, and in the subsequent condensations of other acid hydrazides with imino-ethers, the reaction was always least satisfactory with acetimino-methyl-ether (XXIIa). This was possibly due to the relative instability of this compound in alcohol solution, as compared with the aryl or aryl-alkyl imino-ethers. In no case was an intermediate amidrazone isolated, as the presence of the methoxy groups apparently encouraged rapid ring closure.

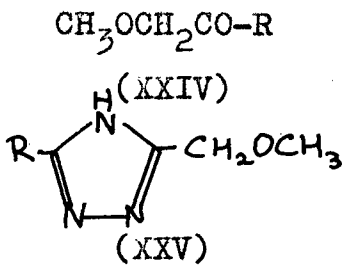
All attempts to isolate any of the free N-unsubstituted-1,2,4-triazole-3-aldehydes after cleavage of the acetals under acidic conditions, have, so far, been unsuccessful.

In weakly acidic conditions, as in the presence of acetic or malonic acids, or with ammonium chloride or pyridine hydrochloride, for varying periods, much of the acetal used was recovered unchanged, on neutralisation and extraction or evaporation of the solution.

(XXIIIc) was not cleaved on refluxing for 4 hours with Girard-T/glacial acetic acid/methanol; nor was any aldehyde detected at any stage when it was kept at room temperature for several weeks with oxalic acid/chloroform.

With stronger acids, such as hydrochloric, sulphuric or phosphoric, cleavage occurred, as shown by the formation of aldehyde derivatives with (N). However, no aldehydes could be extracted from the reactant solutions, after neutralisation with sodium carbonate, the products being apparently very water soluble. Careful evaporation of the aqueous solutions only left crude syrups with no aldehyde activity. The free compounds thus seemed to be very unstable in solution.

(ii) 5-substituted-3-methoxymethyl-1,2,4-triazoles (XXV)



a. R= $-OCH_2CH_3$
b. R= $-NHNH_2$

a. R= $-CH_3$
b. R= $-Ph$
c. R= $-CH_2Ph$
d. R= $-H$

One compound of this type (XXVd) has been previously described (4o), prepared by removal of the -SH group from the corresponding 5-thiol-1,2,4-triazole. This compound has since been prepared by removal of the amino group from the analogous 5-amino-1,2,4-triazole (Section D,IV,iv).

With the exception of the case (XXVd), the condensation of imino-ethers and methoxy-acethydrazides (XXIVb) proved a satisfactory route to 5-substituted-3-methoxymethyl-1,2,4-triazoles. (XXV). Cyclisation occured directly and no intermediate amidrazones were isolated.

Methoxy-acethydrazide (XXIVb).

Ethyl methoxyacetate (XXIVa) was prepared from ethyl chloroacetate ($\frac{M}{4}$) and sodium methoxide ($\frac{M}{4}$), in dry methanol (200 ml) (67); but the product was not isolated from the final methanolic sdution (100 ml). To this was added 100% hydrazine hydrate (15 g), and the mixture was refluxed for 18 hours. The solvent was removed in vacuo, and the residual syrup was washed with ether and then extracted with chloroform. Addition of petrol ether to the chloroform extracts gave white, waxy plates (XXIVb; 13 g; 50% yield calculated from ethylchloroacetate). (Found: C, 34.6; H, 7.5; N, 26.8. $C_3H_8N_2O_2$ requires C, 34.6; H, 7.7; N, 26.9%).

No 1,2,4-triazoles were detected when (XXIVb; 21 g, $\frac{M}{5}$) and formamide (11g, slight excess 1:1) were heated together at 120-160°/2 hours, kept at 160°C/4 hours and finally raised to 180°C for 1 hour. The only product isolated from the dark, syrup reaction mixture was methoxy-acetamide, $CH_3OCH_2CONH_2$ (12 g), b.p. 126-8°C/18 mm, m.p. 92-4°C (Th.m.p. 96°C), as long, flat, white needles from benzene. (Found: C, 40.7; H, 7.7; $C_3H_7NO_2$ requires C, 40.4; H, 7.9%).

3-methoxymethyl-5-phenyl-1,2,4-triazole (XXVb).

Benzimino-methyl-ether hydrochloride (XXIIb.HCl; 3.4 g; $\frac{M}{50}$) was added to a cold solution of sodium hydroxide (0.8 g, $\frac{M}{50}$) in dry methanol (20 ml), and the precipitated sodium chloride rapidly filtered off. The filtrate was added at once to methoxy-acethydrazide (XXIVb, 2.1 g, $\frac{M}{50}$), and the mixture refluxed for 1 hour. The solvent was removed, and the residual syrup extracted with warm benzene (2x 20 ml). Recrystallisation of the benzene soluble

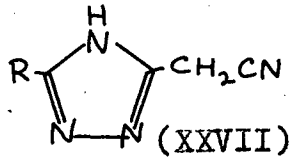
material from benzene/petrol ether gave (XXVb, 1.6 g, 42%) as fine white prisms, m.p. 107-9°C, after drying in vacuo over silica. (Found: C, 64.0; H, 5.9; N, 21.9. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.9; N, 22.2%).

Similarly condensation of (XXIIc) with an equivalent amount of (XXIVb) in methanol, and recrystallisation of the product from benzene/petrol ether or ether/petrol ether, gave (XXVc; 40%), as white needles, m.p. 87-88°C. (Found: C, 64.8; H, 6.5; N, 20.8. $C_{11}H_{13}N_3O$ requires C, 65.0; H, 6.5; N, 20.7%).

When equivalent quantities of (XXIIa) and (XXIVb) were refluxed in methanol for 30 minutes, the product recrystallised from benzene/petrol ether as white prisms, m.p. 110-111.5°C. (XX Va, 80%). (Found: C, 48.1; H, 7.2; N, 33.4. $C_5H_9N_3O$ requires C, 47.3; H, 7.2; N, 33.1%).

III. 5-substituted-3-cyanomethyl-1,2,4-triazoles (XXVII).

$N\equiv C-CH_2CO-NHNH_2$ (XXVI)



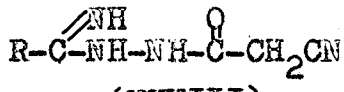
(XXVII)

a. R= $-CH_3$
b. R= $-Ph$
c. R= $-CH_2Ph$
d. R= $-H$

The synthesis of 3-cyanomethyl-1,2,4-triazole (XXVIId) has recently been claimed (42), by heating together formamide and cyano-acethydrazide (XXVI) on a water bath, for several hours. The product was described as a brick red powder, only sparingly soluble in most solvents, m.p. approx. 300°C. (decomp.); but no evidence other than a nitrogen analysis, was given in proof of structure.

As other 3-cyanomethyl-1,2,4-triazoles, described below, are colorless, low melting, and fairly soluble in most organic solvents, the properties described seemed inconsistent with this

structure. Repetition of the preparation gave such a red powder as the only product; and it is suggested that it is most probably a polymer of (XXVIId), or of the assumed intermediate amidrazone (XXVIII; R=-H). On heating other intermediate amidrazones, obtained, (XXVIII a or b) above their melting points, deep red polymers were formed, which decomposed on further ignition. They resembled the compound claimed to be (XXVIId). Ignition of the cyano-methyl-triazoles (XXVII) caused their decomposition to deep red tars.



(XXVIII)

a. R= $-CH_3$
b. R= $-CH_2Ph$.

3-cyanomethyl-5-benzyl-1,2,4-triazole (XXVIIc).

Benzylimino-methyl-ether hydrochloride (XXIIc.HCl, 6.2 g, $\frac{M}{30}$) was added to a cold solution of sodium hydroxide (1.35 g, $\frac{M}{30}$) in dry methanol (60 ml). The precipitated sodium chloride was rapidly filtered off, and the filtrate added at once to (XXVI, 3.3 g, $\frac{M}{30}$) in methanol (10 ml). The mixture was refluxed for 40 minutes, concentrated to 20 ml, and ether (10 ml) was added, precipitating a cream powder (1.2 g, assumed XXVIIIb), m.p. 205-6°C (decomp, to a deep red tarry solid). On attempted recrystallisation from methanol/ether it was progressively converted to (XXVIIc).

Concentration of the original methanol/ether solution gave the main product (XXVIIc), which was charcoaled and recrystallised from ether/petrol ether/and a few drops methanol, as fine white needles (total 4.5 g, 68%); m.p. 147-8°C, after drying in vacuo over silica. (Found: C, 66.5; H, 5.1; N, 28.3. $C_{11}H_{10}N_4$ requires C, 66.7; H, 5.1; N, 28.3%).

Similarly, reaction of (XXIIb) with (XXVI) in methanol gave (XXVIIb; 30%), as fine white needles from ether and petrol ether containing a few drops methanol. After drying in vacuo over silica the product had m.p. 161-3°C. (Found: C, 65.3; H, 4.4; N, 30.4. $C_{10}H_8N_4$ requires C, 65.2; H, 4.4; N, 30.4%). In this case no inter-

mediate amidrazone was isolated, and oily decomposition products were present.

In the analogous consideration between (XXIIa) and (XXVI) in methanol, refluxing for 1o minutes, on concentration and addition of ether a trace only of buff powder was obtained. This was assumed to be (XXVIIIa), m.p. 2oo-2°C (decomp. to a deep red plastic compund). The main product presumed (XXVIIa; 37%) was isolated by evaporation of the solvent, and recrystallisation of the residue from benzene, as fine, white needles, m.p. 133-134.5°C. (Found: C, 5o.o, H, 5.2; N, 44.1. $C_5H_6N_4$ requires C, 49.2; H, 4.9; N, 45.9%). A purer compound could not be obtained. The discrepancy could be partly due to a trace of tightly bound benzene.

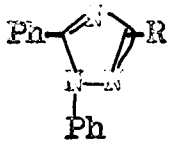
(XXVIIc) was largely recovered unchanged when refluxed for 3 hours with excess of $LiAlH_4$ in ether and the insoluble white precipitate which formed was decomposed with aqueous methanol. A trace of brown oil was the only other material isolated.

(XXVIIc) was also recovered unchanged (35%) from an attempt to condense it with excess formamidine acetate (81) in methanol, and standing for 3 days at room temperature. From the chloroform insoluble part of the reaction products were isolated canary yellow prisms m.p. 147-8°C from methanol and ether. (Found: C, 35.o, H, 7.7; N, 26.4. $C_3H_8N_2O_2$ requires C, 34.6; H, 7.7; N, 26.9%).

These were not identified but were possibly a form or rearrangement product of the, normally white, formamidine acetate, m.p. 162°C. (decomp.), with the same empiric formula. No condensation with the triazole had occured. Formamidine acetate was unchanged on standing alone in methanol for 4 days.

Treatment of (XXVIIc) with conc. H_2SO_4 overnight at room temperature, neutralisation with NaOH, and extraction with chloroform, gave a little white powder, presumably the corresponding amide, m.p. 132-4°C, after recrystallisation from chloroform/petrol ether. Similar hydrolysis of (XXVIIc) with conc. HCl at room temperature overnight gave traces of this same compound, and, as well, a little crude, unstable carboxylic acid.

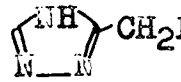
(iv) Bi-triazoles.



(XXIX)

a. R= 

b. R= $-C(=O)-NH-NH-C(=NH)-CH_2Ph.2H_2O$

c. R=  xH_2O

α-form x=3, β-form x=1/2

1,5-diphenyl-5'-benzyl-3,3'-bi-(1,2,4-triazole).

Benzylimino-methyl-ether hydrochloride (XXIIc.HCl, 2.1 g) was added to a cold solution of sodium hydroxide (0.5 g) in methanol (20 ml), the sodium chloride filtered off, and the filtrate added rapidly to a solution of 1,5-diphenyl-1,2,4-triazole-3-carboxylic acid hydrazide (Xc, 3.2 g) in methanol (20 ml). The mixture was refluxed for 30 minutes, and the solvent evaporated off. Addition of chloroform/petrol ether to the oily residue gave a cream powder, probably (XXIXb, 4.0 g, 25-30%) m.p. 114-7°C (decomp.). Recrystallisation four times from chloroform/petrol ether converted this amidrazone intermediate to fine white needles (XXIXc), m.p. 146-7°C (α), resolidifying and remelting at 263-5°C (β). (Found: α form: C, 64.4; H, 5.2; N, 19.6%. $C_{23}H_{24}N_6O_3$ requires C, 63.8; H, 5.6; N, 19.4%. Found: β-form: C, 71.1; H, 4.7; N, 21.5. $C_{23}H_{19}N_6O_{1/2}$ requires C, 71.3; H, 4.9; N, 21.7%).

The lower melting form thus loses 2.5 molecules of water on melting, and is converted to the β-form, which apparently still contains 1/2 molecule water of crystallisation/molecule (XXIXc). Heating (XXIXb) just above its melting point for 2-3 minutes converted it directly to (XXIXc, β).

Similarly reaction of (XXIIb) with (Xc) in methanol gave (XXIXa; 57%) as white powder from benzene/petrol ether; m.p. 238-9°C. (Found: C, 71.6; H, 4.5; N, 22.9. $C_{22}H_{16}N_6$ requires C, 72.5; H, 4.4 N, 23.1%).

This analysis suggests the compound might still contain about 1/4 molecule H_2O per molecule of (XXIXa). ($C_{22}H_{16}N_6 \cdot 1/4\ H_2O$ requires C,71.6; H,4.5;N,22.8%. No amidrazone intermediate was isolated in this case.

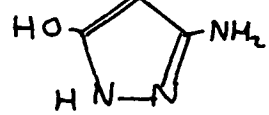
All amidrazones isolated melted with decomposition and were relatively insoluble in organic solvents. The triazoles were far more soluble in organic solvents, and were stable at their melting points.

v) Reactions between imino-ethers (XXII) and acid hydrazides ($RCONHNH_2$), which did not lead to 1,2,4-triazoles.

a) No reaction was detected in attempted condensations between (XXII a or b) and D-gluconic acid hydrazide (87), under the conditions described in the preceding sections. Nor could any triazole be identified in the products of reactions between (XXII b or c) and $CH_3CH_2OCO\text{-}CO\text{-}NHNH_2$ (81)

b) Ethyl cyanoacetate ($NCCH_2COOC_2H_5$) was converted to $CH_3CH_2OCO\text{-}CH_2\text{-}C(=NH)\text{-}OCH_3.HCl$ by the usual treatment with hydrogen chloride/dry methanol/ether (cf.61). Liberation of the free base of this imino-ether, and attempted condensation with formyl hydrazine, under the conditions previously described, did not give rise to any 1,2,4-triazoles. The only condensation product isolated formed deep yellow prisms from methanol; m.p. 207-8°C (decomp.). (Found: C,36.1; H,5.1; N,41.7%. $C_3H_5N_3O$ requires C,36.3; H,5.1; N,42.4%

This compound was identified as 3-amino-5-hydroxy-pyrazole, identical with a sample synthesised by refluxing cyanoacethydrazide (XXVI) with potassium hydroxide in methanol (38).



c) Ethyl cyanoformate ($CH_3CH_2O\ CO\ CN$) was prepared from ethyl oxamate ($CH_3CH_2O\ CO\text{-}CO\text{-}NH_2$) by dehydration with P_2O_5.

Treatment of ethyl cyanoformate (5 g) with hydrogen chloride in methanol/ether gave a white precipitate (4 g), possibly $CH_3CH_2O\text{-}CO\text{-}C(=NH)\text{-}OCH_3.HCl$.

The structure of this compound is dubious. The free base, assumed liberated from this compound by rapid treatment with sodium hydroxide/methanol, could not be shown to give any definite condensation product with either formylhydrazine, or dimethoxy-acethydrazide (XXI).

d) Condensation between equivalent amounts of (XXIIb) and crotonic acid hydrazide ($CH_3CH{=}C(H)C{=}O{-}NHNH_2$) (53), in methanol, under the usual conditions, gave cream felted needles (50-55%) from chloroform/petrol. ether; m.p. 195-6° C (some decomp. ⟶ orange-red liquid). (Found: C, 60.7; H, 6.7; N, 20.1. $C_{11}H_{13}N_3O.3/4\ H_2O$ requires C, 60.9; H, 6.7; N, 19.4%).
The product was not a triazole, but the C:N ratio showed that condensation had occurred. The product was probably the amidrazone (XXXa), with a not very definite amount of water of crystallisation.

(XXX) $CH_3CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}NHNH{-}\overset{NH}{\overset{\|}{C}}{-}R\ .\ x\ H_2O$ a. R = -Ph; b. R = -CH_2Ph

Similar condensation between (XXIIc) and crotonic acid hydrazide gave white crystals (30-35%) from methanol; m.p. 247-8°C. (decomp. to a tarry red liquid). (Found: C, 65.9; H, 6.9; N, 19.5. $C_{12}H_{15}N_3O$ requires C, 66.3; H, 7.0; N, 19.3%). The product was not a 1,2,4-triazole, and was apparently the amidrazone (XXXb; x=0).

Neither of the products (XXXa or b) could be converted to 1,2,4-triazoles by heating or recrystallisation.

e) Condensation between equivalent amounts of (XXIIb or c) and cinnamic acid hydrazide ($PhCH{=}CHCO{-}NHNH_2$) (53), in methanol, did not proceed satisfactorily. In both cases the reaction products formed syrups, from which only traces of crude powders, melting with decomposition, could be isolated. These were possibly amidrazones, of a type isolated in (d). No 1,2,4-triazoles were detected.

Section D.

Section D.

Miscellaneous Reactions; including unsuccessful methods used in the attempted preparation of 1,2,4-triazole-C-aldehydes.

I) Direct substitution on a Carbon atom in the 1,2,4-triazole nucleus.

a) By the -CH=O group.

i) 1,2,4-triazole (I)[59] was reacted with N-methyl-formanilide and phosphorus oxychloride, under the usual conditions for the Vilsmeier reaction (88). Only traces of an aldehyde could be detected in the tarry mixture of reaction products. A few milligrams of this non-steam volatile compound was isolated, as cream needles from ether; m.p. 100-1° C. (Found: C, 66.5; H, 5.7; N, 8.7. $C_9H_9NO_2$ requires C, 66.2; H, 5.6; N, 8.6%). Its crude orange 2,4-dinitrophenylhydrazone derivative had m.p. 240-5° C. Insufficient of this aldehyde was available for identification; but it was not a triazole, and the analysis suggested it might be a diformyl-N-methyl-aniline.

To eliminate any interference from the free -NH- in (I), the reaction was repeated using 4-phenyl-1,2,4-triazole (XL) (60).

No triazole-aldehyde was detected. A trace of the same aldehyde as above was isolated, as the derivative with (N), indicating that it must have derived from starting materials other than the triazoles.

ii) Attempted formylation of (I) or (XL) with dimethyl-formamide/phosphorus oxychloride (cf. 24, 78, 86) gave no trace of any aldehydes.

iii) (I) did not undergo the Reimer-Tiemann reaction with NaOH/chloroform; or as its sodium salt/chloroform. Similar negative results have been reported for 3-hydroxy-1,2,4-triazoles (58).

b) Attempted direct substitution by groups other than -formyl:
i) (I) could not be chloromethylated with paraformaldehyde/ zinc chloride/hydrogen chloride (28).
ii) Unchanged (I) was recovered on attempted bromination of 1,2,4-triazole with bromine/sulphuric acid, and no brominated products were isolated.
(I) did appear to react with bromine/carbon tetra-chloride, in the presence of halogen carriers e.g. iron filings/iodine. The product was a red tar, and appeared a complicated mixture, which was not further studied.
(cf, the halogenation of 1,2,3-triazoles :37).

iii) (I) gave a white precipitate when treated with ethyl magnesium bromide in ether. On reaction of this product with benzoyl chloride, in boiling ether, for five hours, and normal decomposition of the mixture, unchanged (I) was identified by formation of its picrate (m.p. 168°C). No other triazoles were detected.

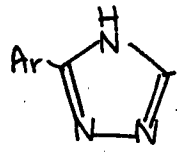
iv) (XL), 1,-phenyl-1,2,4-triazole (59) and 3-bromo-1,2,4-triazole (60) were each treated with n-butyl-lithium in ether (cf 3). In each case the reaction mixture was treated with methyl iodide, or dry ice, or N-methyl-formanilide. In no case could any condensation or desired reaction be detected.

v) The attempted introduction of a diazonium group directly into the 1,2,4-triazole nucleus (cf 32), was unsuccessful. When (I) was treated with mercuric oxide, and sodium nitrite, no compounds were detected which coupled with β-naphthol, under the usual coupling conditions.

vi) There was no apparent condensation between (I) and diphenylformamidine (11,18), fused together at 130°C/3 hours.

vii) No triazole aldehyde was formed on attempted condensation of (I) with chloral hydrate/zinc chloride; followed by treatment with potassium carbonate.

viii) Nitration of 1,2,4-triazoles.



(XLI)

a. Ar= -Ph
b. Ar= $_{p}C_6H_4NO_2$

Nitration of 3-phenyl-1,2,4-triazole (XLI a);(6,64).

Conc. nitric acid (1.2 ml) was added to 3-phenyl-1,2,4-triazole, the mixture cooled, and conc. sulphuric acid (3.0 ml) was added dropwise, with stirring. The mixture was heated on a water bath for 1.5 hours, cooled, and poured into cold water (50 ml). The solution was made alkaline with sodium carbonate, and the yellow precipitate which formed was filtered off. (1.95 g, 70 %).

The product was washed with ether and benzene, and the residue was crystallised from methanol/ ether as fine white needles, m.p. 223-4°C, with some sublimation at the m.p. (Found: C,48.8; H,3.7; N,28.4; O,19.7. $C_8H_5N_4O_2.1/2\ H_2O$ requires C,48.5; H,3.1; N,28.3; O,20.2%). This product was apparently a mono-nitrated derivative of 3-phenyl-1,2,4-triazole, containing 1/2 molecule water of crystallisation per molecule of triazole. Further working up of the crude reaction product indicated that at least 95% was this one compound. Even the most ether-soluble part was this same material, somewhat crude. Any other isomer was present in 5% quantity, if at all. That this nitrated product was 3-p-nitrophenyl-1,2,4-triazole was proved by synthesis of this compound by an unambiguous route:

p-nitrobenzimino-methyl ether hydrochloride (XXIIe) (HCl salt, 1.5 g) was added to a cold solution of sodium hydroxide (0.3 g) in dry methyl alcohol (20 ml). The mixture was filtered rapidly, and the filtrate added at once to a solution of formylhydrazine (1.0 g, excess) in dry methanol (10 ml). After refluxing for 1.5 hours the solution was charcoaled, and the solvent evaporated off. On addition of water containing a few drops of acetic acid

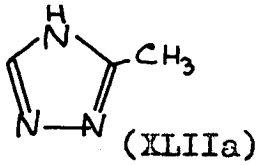
to the syrup residue an orange precipitate formed slowly, and was filtered off after several hours. This was charcoaled and recrystallised from methanol/ether as fine white needles, m.p. 222-3°C (25 mg. XLIb only). A mixed m.p. of this product, with that obtained on mono-nitration of 3-phenyl-1,2,4-triazole was 222-4°C, thus strongly suggesting the compounds were identical. This condensation gave very poor yields, but no other compound could be isolated from tarry by-products. It was concluded that nitration had occured almost entirely in the para-position of the phenyl ring; with a possible trace of attack in the ortho-position. No nitration on the 1,2,4-triazole nucleus was detected. Analogous results have been reported for the mono-nitration of 2-phenyl-1,2,3-triazole (71), and 2 or 4-phenyl iminazole (29,68).

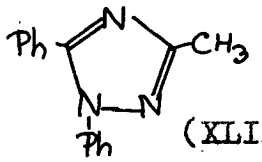
Attempted nitration of 1,2,4-triazole (I) or 3-methyl-1,2,4-triazole (XLIIa) under the conditions used for the nitration of 3-phenyl-1,2,4-triazole (XLIa), gave only unchanged starting materials. No attack on the 1,2,4-triazole nucleus could be detected in either case.

ix) Formylation of 1,2,4-triazole. (cf Section B,12) (4o). 1,2,4-triazole (I, 6.9 g., M/10) and 4o% formalin (25 ml.) were heated at 13o° C in a sealed Carius tube for 2o hours. The clear reaction mixture was evaporated at water pump pressure to a bath temperature of 14o° C, leaving 1o g. syrup. This was treated in aqueous solution, with picric acid, but only a thick yellow syrup precipitated. This was chromatographed on alumina, in acetone. From the first fractions were obtaiend yellow needles (o.3 g.), from methanol/ ether , m.p. 276-8°C. (slight decomp.) On further ignition they exploded violently.
(Found: C, 27.2; H, 1.8; N, 15.8 (Dumas); 13.4 (Kjeldahl) O, 41.9; ash, 1.9%). This compound was not identified, but , if the ash was due to an impurity, the analysis suggested it might be the picrate of an inorganic, nonmetallic compound. Further elution of the chromatogram gave only yellow syrup, which on standing

for several weeks , slowly precipitated yellow prisms, m.p. 160-4°C. These were identified as 1,2,4-triazole picrate (Th.m.p. 168°C) (7). Similarly, if isolation was attempted via the HCl salt, the only one isolated was that of (I) (m.p. 169°), which liberated free (I) on treatment with $NaHCO_3$.
When the reaction mixture was distilled directly at an oil pump, after initial removal of low boiling fractions at a water pump, the only sharp fraction had b.p. 152°C/1mm, and solidified at once to nearly pure (I), m.p. 116-120°C. No fraction of b.p. 140°/1mm , reported for 3-hydroxymethyl-1,2,4-triazole(40), was detected.

II. Attempted formation of 1,2,4-triazole-C-aldehydes from 3-methyl-1,2,4-triazoles.


(XLIIa)


(XLIIb)

a) By oxidation.

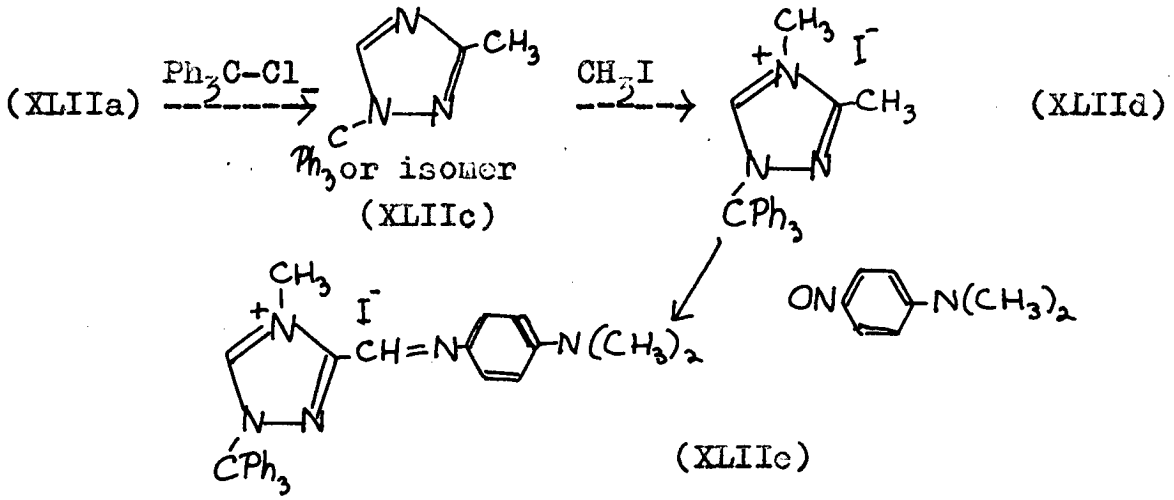
No aldehydes could be detected on attempted oxidation of (XLIIa) with chromium trioxide/glacial acetic acid/conc. sulphuric acid, and either acetic anhydride or propionic anhydride. Nor was (XLIIa) apparently oxidised by sodium persulphate/silver nitrate (cf 12); nor by manganese dioxide in chloroform.

The attempted oxidation of (XLIIb) (4) with chromyl chloride in chloroform (45) failed; thus confirming the observations of Atkinson (5). Nor was (XLIIb) oxidised to an aldehyde by either lead tetraacetate in glacial acetic acid (cf 77), or by selenium dioxide in ethanol. Selenium dioxide has been reported not to oxidise 1-phenyl-3,5-dimethyl-1,2,4-triazole (58).

(XLIIb) was recovered unchanged after refluxing for 12 hours with N-bromo-succinimide in carbon tetrachloride.

b) By attempted formation of a Schiffs' base.

The projected reaction route was as follows:



(XLIIe) might then possibly have been hydrolysed, dequaternised, and the trityl group removed. The quaternisation of the triazole would activate the normally inert C-methyl group, to some extent. Coupling of such an activated group has been described in the formation of cyanine dyes containing the 1,2,4-triazole nucleus (2o), but reaction only proceeded with some difficulty.

3-methyl-1,2,4-triazole (XLIIa). Small quantities were prepared by removal of the -SH group from 3-methyl-1,2,4-triazole-5-thiol with nitric acid (4o), but this reaction did not occur as readily as stated. The main product generally had m.p. 295-300°C, and was probably a dithiol dimer. Removal of the -thiol group with 100 vol. hydrogen peroxide gave a higher yield of (XLIIa). However, the most convenient preparation of (XLIIa) was via the reaction of aminoguanidine sulphate and glacial acetic acid to give 3-methyl-5-amino-1,2,4-triazole (85); followed by removal of the amino group by diazotisation in the presence of hypophosphorous acid (3o). The yield was 50% (XLIIa), based on aminoguanidine sulphate used, of a product m.p. 96-8°C. after sublimation (Lit. 94°C). This method has been used for the synthesis of 3-ethyl-1,2,4-triazole (1o).

1-trityl-3-methyl-1,2,4-triazole (XLIIc), or isomer.

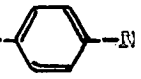
To dry (XLIIa; 2.0 g) in absolute methanol (15 g) was added sodium (0.5 g; 1:1). The mixture was evaporated to dryness on a water bath, in vacuo; and finally in an oven at 85°C, until no trace of methanol remained. To the residue was added sodium dried benzene (30 ml) and trityl chloride (6.0 g) and the mixture was refluxed for two hours. The solution was filtered, the residue washed with warm benzene, and much of the benzene evaporated off from the combined filtrates; Cooling and addition of ether gave cream needles or prisms, m.p. 195-6°C. (XLIIc, or isomer; 3.7 g, 54%) (Found: C, 81.3; H, 5.9; N, 13.8. $C_{22}H_{19}N_3$ requires C, 81.2; H, 5.9; N, 12.9%).
The position of the trityl group in the triazole nucleus is not certain, although the formula indicated is assumed the most likely.

In a repeat preparation, using the same quantities, 5.5 g cream prisms were obtained from benzene /petrol ether; m.p. 135-6° C. (Found: C, 84.5; H, 6.0; N, 7.5; O, 2.3 . $C_{41}H_{35}N_3O$ requires C, 84.1; H, 6.0; N, 7.2; O, 2.7%). This analysis suggests that the product was a 1:1 adduct of (XLIIc) and triphenyl carbinol (Ph_3-COH). Mild treatment of the assumed adduct with hydrochloric acid in ethanol solution gave free triphenyl carbinol. Production of such an adduct from the second run, and not from the first was unexpected.
Similar tritylation of (I) gave 1 (4)-trityl-1,2,4-triazole, as white prisms from benzene ether; m.p. 210-1°C, with slight sublimation as fine needles. (Found: C, 81.2; H, 5.4; N, 13.7 $C_{21}H_{17}N_3$ requires C, 81.0; H, 5.5; N, 13.5%).

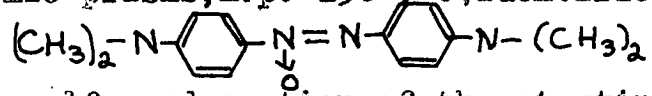
Quaternisation of (XLIIc)

To (XLIIc, 3.25 g) in sodium dried benzene (30 ml) was added methyl iodide (3 g), and the mixture refluxed for 4 hours. The product (assumed XLIId, or isomer, 1.38 g) was filtered off as bronze plates, and washed with benzene, m.p. 185-190°C (darkening to form a deep scarlet liquid, with decomp. on further ignition).

Treatment of the reaction mixture with more methyl iodide gave a further 0.68 g (XLIId, Total 2.06 g, 44%).
The product partially decomposed on attempted recrystallisation; the color varied from deep yellow, to vermilion, to brown; and even the melting point varied, apparently with rate of heating, from 185-213°C. (Found: (I⁻, 27.5%; $C_{23}H_{22}N_3I$ requires (I⁻, 27.2%).
The exact position of quaternisation, and of the trityl group, in this compound is unknown. The formula (XLIId) is assumed the most likely.

Attempted condensation of (XLIId) with ON-  -$N(CH_3)_2$.

To (XLIId, 2.0 g) in absolute methanol (30 ml) containing 3 drops piperidine, was added p-nitroso-dimethylaniline (0.66g, 1:1), and the mixture was refluxed for 5 hours. The reaction mixture was cooled and filtered, leaving 0.3 g black plates. These were washed with ether, and recrystallised from petrol ether to give bronze prisms, m.p. 256-8°C; identified as:



produced by self-condensation of the starting material. (Found: C, 67.9; H, 7.0; N, 19.7. $C_{16}H_{20}N_4O$ requires C, 67.6; H, 7.0; N, 19.7%). Evaporation of the methanolic filtrate gave only a black tar, from which no other compounds could be isolated. No sign of the desired condensation, to form a Schiff's base, could be detected, and this route was therefore not further studied.

III. Attempted formation of 1,2,4-triazole-C-aldehydes from 3-hydroxymethyl-1,2,4-triazoles.

In addition to the successful routes previously described (Section B), several methods tried did not give rise to aldehydes.

The isomeric alcohols (IIIa, A or B), underwent the same reactions.

Oxidation of (IIIa) with alkaline potassium permanganate, or potassium dichromate/sulphuric acid, gave only the acid (Xa), and much tar.

There was no apparent oxidation reaction when (IIIa) was treated with conc. or dilute nitric acid; sodium arsenate/hydrochloric acid or arsenic pentoxide/aqueous ethanol. Nor was there detectable reaction of (IIIa) with cupric oxide/300°C; potassium periodate/aqueous ammonia; periodic acid in methanol; or aqueous cupric acetate.

No oxidation of (IIIa) took place with manganese dioxide in petrol ether. However, on addition of some carbon tetrachloride, and standing for 3 days at room temperature, a trace of oxidation was detected, although the greatest part of the alcohol was unchanged. A few milligrams of the acid (Xa) was isolated, and even less of the aldehyde (IVa), identified as its derivative (IVa_3). This method was of no preparative value.

Reaction of (IIIa) with thionyl chloride, and evaporation of excess reagent, left crude, acrid crystals, m.p. 148-153°C (decomp), assumed to be the corresponding 3-chloromethyl-triazole (Xk). No Grignard compound could be formed on treatment with magnesium iodine in dry ether. The assumed (Xk) did not undergo the Sommelet reaction (cf 84) with hexamethylenetetrammine in chloroform, followed by hydrolysis with acetic acid.

IV. Other reactions.

i) 3-amino-1,2,4-triazole, diazotised in dilute sulphuric acid, did not react with formaldoxime, under the conditions used for 3-amino-pyridine (13). The -CH=NOH group could thus not be introduced into the 1,2,4-triazole ring in this way, under the conditions tried.

ii) 3-amino-1,2,4-triazole, diazotised as in i) did not appear to react with cuprous cyanide, with or without sodium cyanide, in neutral or alkaline solution. Nor could any triazole nitrile be detected in an attempted reaction with HCN.

iii) No formation of 3-cyano-1,2,4-triazole could be shown when 3-bromo-1,2,4-triazole was fused with cuprous cyanide at 180-190° C/2hours (cf 48). An adduct containing the inorganic metallic salt appeared to form.

iv) The attempted synthesis of new 1,2,4-triazoles from amino-guanidine salts.

Several 3-amino-5-substituted-1,2,4-triazoles have been synthesised from amino-guanidine salts, and suitable acids or derivatives, under varying conditions. (6, 51, 69, 70, 85). In general the substituent in the 5-position was an alkyl, aryl, or other inert group, which did not interfere with the course of the reaction. Some attempts have been made to synthesise triazoles with other groups in the 5-position, by this method.

It has been reported (58) that amino-guanidine sulphate did not form triazoles with dichloroacetic acid or tartaric acid. No evidence of 1,2,4-triazole formation could be found when amino-guanidine sulphate was reacted under the usual conditions with gluconic acid, stearic acid or stearamide; nor with p-nitrobenzoic acid/HBr.

No product was isolated from an attempted reaction between amino-guanidine sulphate and phenylacetic acid, in the presence

of water, and a few drops of conc. nitric acid. When equivalent amounts of these reactants (0.2 mole each) were refluxed together for 19 hours in the presence of a slight excess of 48% hydrobromic acid (35 g), a thick syrup formed. The only product which could be isolated was transparent prisms (2.0 g) from ethanol/ether; m.p. 102-4°C (Found: C, 65.5; H, 5.8; N, 18.4. $C_{17}H_{18}N_4O_2$ requires C, 65.7; H, 5.8; N, 18.1%).

While there was no proof of structure, this analysis and observed properties were consistent with the formula

$$PhCH_2CO\text{-}NHNHC(=NH)\text{-}NH\text{-}CO\text{-}CH_2Ph$$

On reaction of amino-guanidine sulphate (12.3 g; 0.1 m) and lauroyl chloride (0.1 m) in dry pyridine (150 ml) at -10°-0° C, the only isolated product was a waxy solid (7 g), m.p. 52-4° C, to an opaque oil, m.p. 85-8° C.

(Found: C, 68.5; H, 11.2; N, 13.3. $C_{25}H_{50}N_4O_2$ requires C, 68.4; H, 11.5; N, 12.8%).

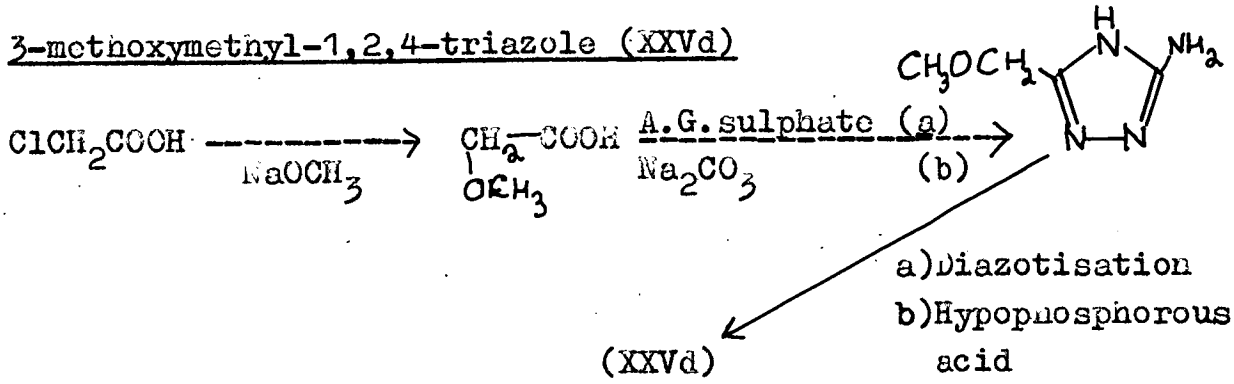
This analysis could agree with a structure analogous to that above, viz.

$$CH_3(CH_2)_{10}CO\text{-}NHNH\text{-}C(=NH)\text{-}NH\text{-}CO\text{-}(CH_2)_{10}CH_3$$

It is possible that adjustment of reaction conditions, for example by the use of an excess of amino-guanidine bicarbonate, might give the desired 1:1 addition; but the reaction was not studied further.

No 1,2,4-triazoles were detected in any of these reactions.

3-methoxymethyl-1,2,4-triazole (XXVd)



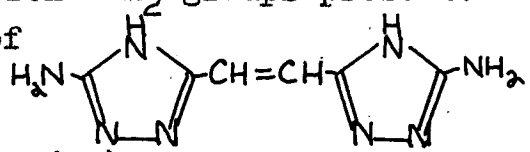
Methoxy-acetic acid was prepared in 69% crude yield from chloroacetic acid, using the method described for the preparation of ethoxy-acetic acid (27). The acid obtained on evaporation of the ether extract was used directly, without preliminary distillation.

Methoxy-acetic acid (9.0 g., M/10) and amino guanidine sulphate (12.3 g; M/10) plus a few drops of conc. nitric acid, were heated together at 100-105°C/ 16 hours. The reaction mixture was made just alkaline with aqueous sodium carbonate, and evaporated to dryness several times, until all the transient purple color had discharged. The cold residue was extracted several times with methanol, and the extracts evaporated, leaving a thick syrup which set to a hard glass (10.8 g). Treatment with methanol/ether gave clusters of low melting needles in an oily background. This assumed 3-methoxymethyl-5-amino-1,2,4-triazole (10 g) in water (10 ml.), conc. H_2SO_4 (3 ml.) and 30% hypophosphorous acid (15g.), was diazotised at 35-8°C., by the dropwise addition of sodium nitrite (5.5 g.) in water (10 ml.). After a further 10 minutes at 35°C. nitrogen evolution had ceased, the mixture was made alkaline with sodium carbonate, evaporated to dryness. Extraction with chloroform, and evaporation of the solvent, left waxy cream needles (XXVd,, 2.55 g, 29%) from methanol/ether; m.p. 55-9°C. (Found: C, 41.9; H, 6.2; N, 37.9. $C_4H_7N_3O$ requires C, 42.5; H, 6.2; N, 37.2%).

(XXVd) has been previously synthesised by a different route (4o), as needles m.p. 65-6°C. In view of the poor yields and inferior quality of the product from the above reaction, the method was not further investigated. (XXVd) was not hydrolysed to 3-hydroxymethyl-1,2,4-triazole on refluxing with conc. hydrobromic acid; in agreement with the previous workers (4o).

1,2,4-triazole-3-aldehyde dimethyl acetal could not be made by this method. The necessary starting material, dimethoxy acetic acid, although known as esters or salts, is unstable in the free state, due to the sensitivity of the acetal group at acid pH. Attempts to liberate the acid and react it rapidly with amino guanidine bicarbonate gave rise to syrups only. No triazoles could be detected; nor was any precipitate obtained with 2,4-dinitrophenylhydrazine/ethanol/HCl, suggesting that liberated aldehydes had condensed with $-NH_2$ groups present.

The synthesis of



has been claimed (76), by condensation of an amino-guanidine salt and crotonic acid, and evaporation of the reaction mixture to dryness with potassium carbonate. That this acid was used seems to be an error in a review article (66), as the patent was not available, and the name of the acid is not stated in the abstract. Presumably maleic acid was meant. Other workers (43) have found that 1,2,4-triazoles do not form in reactions, as above, of amino-guanidine salts and β-unsaturated carboxylic acids. This was confirmed for the attempted reactions between amino guanidine bicarbonate and crotonic acid or maleic acid.

Section E.

Section E

Infra-red and ultra-violet spectra of 1,2,4-triazoles.

I. Infra-red spectra.

Few infra-red spectra of 1,2,4-triazoles have been described in the literature, other than those of the parent compound (57), and N-acylderivatives (56). Recent spectral measurements on 3-hydroxy and 3-thiol-1,2,4-triazoles have shown that they exist as the oxo or thione forms, respectively, both as solids or in solution (109). This is in agreement with their chemical properties, and with other physical evidence (9,34).
Spectra of some N-unsubstituted-1,2,4-triazoles have been determined by Potts (46,65,66), but details have not yet been published.

Infra-red spectra of 1,2,4-triazoles are currently being investigated in this department, and the spectra of a number of 1,5-diaryl-triazoles, described in sections A and B, have been determined. At this stage no attempt has been made to analyse the results in detail, or to correlate bands present with vibrations of the phenyl or 1,2,4-triazole rings. Emphasis was placed on assigning bands due to the groups in the 3-position, notably the aldehydes. The presence of the aldehyde group in these compounds was clearly demonstrated (a).

For the six 3-substituted -1-p-tolyl-3-phenyl-1,2,4-triazoles studied, variations in their spectra should be due to the group in the 3-position. Many of the characteristic bands expected were readily identified, and their positions were in good agreement with values assigned to specific vibrations of similar groups in other series (b). Unless otherwise stated, the expected ranges of band positions are those given by Bellamy (100).

The spectra of 1,5-diphenyl and 1,5-diphenyl-3-methyl-1,2,4-triazole (XLIII and XLIIb) were compared with those of these other 1,5-diaryl-3-substituted-triazoles. When allowance was made for specific absorptions by additional groups present, it could be said, to a first approximation, that most of the main bands visible in (XLIII) or (XLIIb), were present throughout the series.

Experimental.

The instrument used was a Perkin-Elmer infra-red double beam spectrophotometer, No. 221. Unless otherwise stated spectra were obtained using KBr discs. Spectra measured on samples in KBr or Nujol did not vary much.

The main bands in the spectrum of 1,5-diphenyl-1,2,4-triazole were as follows (cm^{-1}).

3230 moderate, 3090 strong, 3070 m, 1635 m, 1615 m, 1595 s, 1587 m, 1575 m, 1500 v.s., 1482 s, 1454 s, 1445 s, 1436 s, 1427 s, 1378 s, 1369 s, 1292 m, 1285 m, 1274 m, 1263 s, 1197 s, 1177 m, 1137 s, 1068 s, 1023 m, 1001 m, 983 s, 927 m, 920 m, 914 m, 845 m, 778 s, 766 v.s., 738 m, 718 v.s., 701 s, 690 v.s. 678 s, 670 s.

The band at 3090 cm^{-1} was assigned to the C-H stretching vibration in the 1,2,4-triazole ring, which absorbs near 3060 cm^{-1} in spectra of other N-hetero-aromatic compounds (100, 103). It is absent in the spectra of 3-substituted triazoles. The spectrum of 1,5-diphenyl-3-methyl-1,2,4, triazole was almost identical with that above, but for the omission of the bands at 3090, 1436, 1369, 1263, 1197, 1137, 973, 920, 701 and 670 cm^{-1}, and occasional shifts of less than 5 cm^{-1}. Additional bands were present at 2970 m, 2930 m, 1410 s, 3975, 1335 s, 1089 m, and 1030 m cm-1

Some of these could be ascribed to vibrations of the $-CH_3$ group, which produces bands due to C-H stretching near 2960 cm^{-1}, and to C-H deformation near 1430 and 1380 cm^{-1} (100, 103).

Bands underlined were present in most of the other 1,5-diaryl-1,2,4-triazole spectra examined, and most other bands were present in at least some of the spectra.

a) Infra-red spectra of 1,5-diaryl-1,2,4-triazole-3-aldehydes.

The presence of an aldehyde group in a molecule can be shown by the appearance in the infra-red spectrum of bands due to the carbonyl stretching absorption, associated with ones due to C-H stretching. The range of frequencies for the strong carbonyl bands fall within narrow limits, which shift only slightly with different types of compound, e.g. 1715-1695 cm^{-1} for aryl aldehydes, and 1705-1680 cm^{-1} for α-β-unsaturated aldehydes. All the 1,2,4-triazole-aldehydes had at least one strong absorption band between 1740 and 1705 cm^{-1}, with additional weaker bands nearby (Column 1). The C-H stretching vibrations generally show as weak bands between 2900 and 2700 cm^{-1}. Weak bands in this region were observed in all the 1,2,4-triazole-aldehyde spectra (Column 2).

Compound	C=O Absorption cm^{-1} strong bands	weaker b.	2. C-H stretching absorpt. cm^{-1} weak bands.
IVa	1740 ;	shoulder at 1680w	2840, 2820, 2780, 2720 v.w., 2680 v.w.
IVb	1720, 1711	Equal intensity	2920, 2840, 2790, 2720 v.w., 2680 v.w.
IVc	1706	1685m	2925, 2870, 2810
IVd	1717	1670w	2960, 2925, 2860 m, 2790
IVe	1710	1682m-w	3020, 2970, 2940, 2910 v.w. 2875, 2840 m, 2780.
IVf	1710	shoulder at 1670w	2840, 2790
IVg	1710	1670w	2850

A weak band due to hydrogen deformation of the CHO group may be present near 900 cm^{-1} (100). A moderate to weak band at 931-923 cm^{-1} occurred in the spectra of all the 1,2,4-

triazole-aldehydes; but as it was present in the spectra of most of the triazoles examined it could not be ascribed to this vibration. An additional weak band at 910 cm^{-1} did appear in the spectrum of (IVc).

(IVe) showed a strong band at 1260 cm^{-1}, due to the asymmetrical C-O-C stretching vibration, which absorbs near 1250 cm^{-1} in arylalkyl ethers (100, 102).

In neither (IVf) nor (IVg) was there any evidence of a band which could be assigned to the C-Br linkage. Such absorption may occur in the region 650-500 cm^{-1} (100, 103). Apart from the C-H stretching bands no aldehyde showed any significant absorption between 4000 and 1800 cm^{-1}.

b) The infra-red spectra of 3-substituted-1-p-tolyl-5-phenyl-1,2,4-triazoles.

In the six spectra of this type determined, variations were assigned to vibrations of the groups in the 3-position. Absorptions due to the aryl or triazole rings have been omitted.

1) 1-p-tolyl-5-phenyl-1,2,4-triazole-3-aldehyde (IVb).

showed absorptions at 2920, 2840, 2790, 2720, 2680, 1720, 1711, and 930 cm^{-1}. The significance of these bands has been discussed in section (a).

2) 1-p-tolyl-5-phenyl-3-hydroxymethyl-1,2,4-triazole (IIIb).

The most characteristic band in alcohol spectra is that between 3700 and 2500 cm^{-1}, arising from the OH stretching vibration. It has been possible to correlate the position and nature of the observed band, to some extent, with the degree and type of hydrogen bonding, if present (100).

The spectrum of (IIIb) in KBr or Nujol showed a strong broad band at 3180 cm^{-1}. This suggested the presence of hydrogen bonds, stabilised by resonance, which absorb in the range 3200-2500 cm^{-1}, although such a band is usually weaker in intensity. Intermolecular polymeric association can give rise to a strong broad band between 3400 and 3200 cm^{-1}; but such bonding could not readily occur with this type of alcohol. There was no indication of any free OH, which would give a sharp band near 3600 cm^{-1}. The nature of the hydrogen bonding present in the 1,5-diaryl-3-hydroxymethyl-1,2,4-triazoles is further discussed in Section E III.

Most alcohols show two more bands at lower frequencies, which are assigned to C-O stretching and OH deformation modes. In primary alcohols these appear as strong bands near 1050 cm^{-1}, and between 1380 and 1250 cm^{-1} (100).

Strong bands at 1051 and 1356 cm^{-1} were present in the spectrum of IIIb, in KBr. The other stable alcohols showed similar bands in KBr or Nujol. In each case the OH stretching band determined from a Nujol mull, was broader and slightly weaker than that observed from a KBr disc.

Reference number	KBr disc			Nujol Mull		
	OH stretching	C-O stretching	OH deformation	OH stret.	CO stret.	OH deform.
		cm^{-1}			cm^{-1}	
IIIaB	3190	1354	1050 cm^{-1}	3180	1350	1056
IIIb	3180	1356	1051	3180	1355	1055
IIIc	3210	1350	1051	3190	1357	1055
IIId	3225	1356	1043	3210	1358	1049
IIIe	3180	1349	1052	----	----	----

3) 1-p-tolyl-5-phenyl-1,2,4-triazole-3-carboxylic acid (XIa)

i) OH-stretching vibrations of carboxylic acids show as broad bands in the region above 2500 cm^{-1}. The most significant region is 2700-2500 cm^{-1}, where few other vibrations absorb. The spectra of (XIa, XVIa and XVIIa) showed continuous absorption from 3350 to 2500 cm^{-1}, with a few superimposed peaks, but little detail. The maximum absorption of (XIa) in this region was at 3050 and 2950 cm^{-1}, with smaller peaks and at 2725m, 2660 w and 2580 w. Such bands indicate dimerisation, and the presence of strong hydrogen bonds (100, 101, 102).
ii) C=O stretching vibrations of carboxylic acids absorb strongly in the range 1725-1700 cm^{-1} for saturated acids, 1715-1690 cm^{-1} for α-β-unsaturated acids, and 1700-1680 cm^{-1} for aryl acids. The spectrum of (XIa) determined in KBr or Nujol; had a broad, strong band at 1708 cm^{-1}, with shoulders at 1735 and 1718 cm^{-1}. This band was at 1730 and 1725 cm^{-1} in the spectra of (XVIa) and (XVIIa), respectively.
iii) The vibration spectra of carboxylic acids are complex below 1500 cm^{-1}, largely due to the coupling of the C-O stretching and O-H bonding motions. These often produce a weak band near 1420 cm^{-1}, and a strong band in the region 1320-1210 cm^{-1} (100, 101, 102, 103). A band of medium intensity was present at 1420 cm^{-1} in the spectrum of (XIa) and at 1415 cm^{-1} in those of (XVIa) and (XVIIa). This band was absent in the spectrum of the ester (XIb). A strong, broad band was observed at 1232 cm^{-1} in the spectrum of (XIa), and at 1215 cm^{-1} in those of the ortho and meta-tolyl isomers.
A weak band may occur between 950 and 900 cm^{-1}, due to CH out-of-plane bending vibrations. A medium band was present at 920, 925 and 924 cm^{-1} in the spectra of the o, m, and p-tolyl acids respectively; but absorption at this frequency was present in most of the triazole spectra.

4) 1-p-tolyl-5-phenyl-1,2,4-triazole-3-acrylic acid (XXb).

The spectrum of (XXb) was similar to that of (XIa) at higher frequencies. There was continuous absorption, with subsidiary peaks, between 3100 and 2200 cm^{-1}, due to OH and CH stretching vibrations. The strong C=O stretching band was present at 1690 cm^{-1}, within the range of 1715-1690 cm^{-1}, quoted for α-β-unsaturated acids (100).

A medium to strong band was present at 1403 cm^{-1}. This could be due to the coupled C-O and O-H vibrations described in (3) above, but the band intensity is usually weaker. It may also arise from in-plane C-H bending vibrations (cis), which absorb at 1420-1400 cm^{-1}.

C-H out-of-plane deformations occur near 970 cm^{-1} for trans and 690 cm^{-1} for cis alkenes. In the spectrum of (XXb) the strong band at 689 cm^{-1} could not be ascribed to this source, as it was present in most of the spectra examined, and may arise from vibrations of the mono-substituted aromatic ring.

A medium band present at 970 cm^{-1} might be attributed to such a trans vibration.

5) 1-p-tolyl-5-phenyl-1,2,4-triazole-3-carboxylic acid methyl ester (XIb).

Esters have two characteristic absorption bands, arising from the C=O and C-O stretching vibrations respectively. The former is present in aldehydes, ketones and acids; and the latter also in alcohols and ethers.

i) C=O stretching.

A strong band was present at 1740 cm^{-1}. This value may be compared with ranges of 1730-1717 cm^{-1} for α-β-unsaturated or aryl esters; 1750-1735 cm^{-1} for saturated esters; and 1770-1745 cm^{-1} for esters with an electronegative substituent in the position (100).

ii) The C-O stretching vibrations may produce one or two strong bands within the range 1300-1000 cm^{-1}, but the exact position is dependant on the nature of other groups present. Strong bands were present at 1215 and 1175 cm^{-1}, in the spectrum of (XIb).

There was no significant absorption in the OH-stretching region near 3000 cm^{-1}, where intense bands occur in the carboxylic acid spectra.

6) 1-p-tolyl-3-phenyl-1,2,4-triazole-3-carboxylic acid hydrazide (XIc).

The $-CO-NHNH_2$ group was treated as essentially a secondary amide for interpretation of the infra-red spectra. Effects of the presence of the $-NH_2$ group were also considered.

The main characteristic band of amides (Amide I) is that due to the carbonyl absorption, and lies between 1700 and 1630 cm^{-1}. A weaker band (Amide II) is found in primary and secondary amides in the range 1570-1470 cm^{-1}, usually near 1540 cm^{-1}. It is often, though inconclusively, assigned to a N-H deformation vibration (1oo, 1o2).

The spectra of (XIc) and (XVIc) each showed a strong band at 1680 cm^{-1} and a moderate band at 1540 cm^{-1}. Both amide and amine spectra show bands between 3500 and 3050 cm^{-1}, which are assigned to N-H stretching modes. In the spectrum of (XIc) a strong broad band was present between 3550 and 2900 cm^{-1}, with a maximum at 3400 cm^{-1}, and subsidiary peaks at 3525, 3450, 3360, 3028 and 2920 cm^{-1}.

A similar band was observed in the spectrum of (XVIc). Doublets, at 1122, 1112 cm^{-1} and at 1135, 1115 cm^{-1} in the spectra of (XIc) and (XVIc) may be caused by C-N stretching vibrations, which in aliphatic amines absorb between 1220 and 1020 cm^{-1}. Such absorption may also occur near 1410 cm^{-1} (1oo, 1o2).

A moderate band was present at 1400 cm^{-1} in the spectrum of (XIc), and at 1405 cm^{-1} in that of (XVIc).

Primary and secondary amines show bands due to NH - deformation, between 1650 and 1570 cm^{-1}. No bands in this region were observed in the spectra of triazole acid hydrazides, which were not also present in those of other 1,5-diaryl-1,2,4-triazoles.

The acyclic intermediates.

The spectra of the acyclic intermediates (VII d, and $VIIb_2$), which corresponded to the triazole acid hydrazides (XIc and XVIc), were determined. They resembled each other very closely, but were quite different from those of the cyclic compounds. All four spectra showed considerable absorption between 3600 and 2900 cm^{-1}, but this region was not suitable for comparison, as the bands overlapped to a great extent. The main bands visible below 2900 cm^{-1} in the spectrum of ($VIId_1$) were at:

1620 s (C=O stretching), 1575 s, 1530-1435 s, 1327 m, 1291 m, 1254 s, 1195 s, 1175 s, 1120 m, 1110 m, 1030 m, 965 v.s., 892 m, 870 s, 815 v.s., 795 s, 750 m, 702 v.s., 681 s.

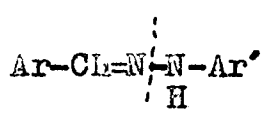
The bands at 750 and 702 cm^{-1} were those shown by a mono-substituted aromatic ring, and were also present in the triazole spectra. The expected ranges were 770-730 and 710-690 cm^{-1}, respectively. (100).

The band at 815 cm^{-1} was that shown by para-substituted aromatic compounds, in the range of 860-800 cm^{-1}. It was present in the spectrum of (XIc) at 820 cm^{-1}, and was absent in the ortho-substituted compounds ($VIIb_2$ and XVI c).

II. Ultra-violet spectra.

The ultra-violet spectra of many 1,2,4-triazoles have been previously determined (8,9,66,79,106,107). The spectra of the 3-substituted-1,5-diaryl-1,2,4-triazoles varied little with substituents. The bands were broad, and the maxima could not be located sharply. All showed strong absorption at wavelengths below 260 mμ ($\log \varepsilon$ 4), and the transmission increased rapidly to 100% between 260 and 290mμ.

Grammaticakis and Ramart-Lucas (104,105) have studied the spectra of many nitrogenous organic compounds, including some whose ultra-violet spectra show analogies with those of the 1,5-diaryl-triazoles. These include the 1,5-diphenyl-1,2,3-triazoles, phenylhydrazones and N-acyl-phenylhydrazones of aromatic aldehydes, and diaryl-triazenes (104,105). In these compounds there are at least two sets of uncoupled chromophores, each contributing to the final spectrum e.g.



Each spectral curve may be regarded as the resultant of two or more high intensity absorption bands, which are identified as E bands below 230 mμ, and K bands at higher wavelengths, on Braude's views (108). Low intensity benzenoid absorption, occurring near 270 mμ, may be masked by a K band. This was the case in all the 1,5-diaryl-1,2,4-triazole spectra examined, and no fine structure was visible.

1,2,4-triazoles containing only one phenyl group show one intense K band, due to the conjugation of the benzene and triazole chromophores (9). This is the case irrespective of the location of the phenyl group; although the more extended conjugation possible with a C-phenyl link is shown by the higher intensity and λ max. of the 3-phenyl triazole.

Such conjugation in the 1 or 4-phenyl triazoles is possible in the ionic forms only. When two phenyl groups are present in the 1,5 positions on the triazole nucleus, it can be shown from models that all three rings cannot be planar. Conjugation with the triazole ring will be much greater with the 5-phenyl than with the 1-phenyl group, and there is no tendency for them to show any stilbene-like conjugation with each other, through the triazole ring. The group which is uncoupled from the triazole ring acts as an isolated chromophore. The resulting spectrum may contain two maxima, or, with greater overlapping, one may appear as a shoulder.

When a 3-CH_2OH group is present on the triazole ring the -OH is isolated from the chromophoric group by a methylene bridge, and cannot modify it to any extent. The spectrum of (IIIaB) thus closely resembles that of (XLIIb), which has λmax =252 mμ ; log ε max = 4.02 (9). The spectra of the 1,5-diaryl-1,2,4-aldehydes resembled those of the corresponding alcohols in shape. Differences in extinction coefficients were slight, and not consistent throughout the series. This was not unexpected, considering the structure of these triazoles, and the first order conjugation present. The spectra of the, as yet unknown, 1,3-diaryl-1,2,4-triazole-5-aldehydes should, however, show a bathochromic and hypsochromic shift relative to those of the corresponding alcohols. In this case steric hindrance would be reduced, and second order conjugation would be present.

In the case of the 1-p-tolyl-5-phenyl-1,2,4-triazoles the presence of a carboxylic acid, carboxylic ester or carboxhydrazide group in the 3-position all had the same effect of producing smooth sloping curves, with no maxima above 210 mμ. The intensity of absorption was greatest for the hydrazide and least for the ester. The introduction of a

3-C(H)=C(H)-COOH group had a similar effect, but due to the increased conjugation there was a uniform bathochromic shift of about 20 mμ. There were two very slight maxima and the absorption dropped sharply between 280 and 310mμ.

The introduction of a methyl group in the meta position of the 1-phenyl group in (IIIa) or (IVa) had little effect on the ultra-violet spectrum. A para-methyl group caused broadening and flattening of the maxima, and a slight hypsochromic shift was observed in both bands. In none of the 3-substituted -1-ortho-tolyl-5-phenyl-1,2,4-triazole spectra was more than one intense band observed above 210mμ This might be due to steric hindrance interfering with the resonance of one of the sets of chromophores. The absorption band was still at a sufficiently high wavelength to obscure any fine structure. In the aldehydes or alcohols the presence of a para-bromo or para-methoxy group in either benzene ring caused a bathochromic shift in both bands. Except in the case of (IIIe) the extinction coefficients were also raised.

The ultra-violet spectra of the intermediates ($VIIb_2$) and ($VIId_1$) were quite different from those of any of the 1,2,4-triazoles. In each case three bands were present which only overlapped slightly, and formed distinct maxima. Two of these maxima, near 290mμ and 340mμ were at wavelengths where little or no absorption was present in the triazoles.

Ultra-violet data given in this section were obtained using a Perkin-Elmer 4000 A Spectracord; and those given in other sections from a Unicam S.P.500 Spectrophotometer. Methanol was used as solvent, throughout.

Ultra-violet Spectra of 3-substituted-1,5-diaryl-1,2,4-triazoles.

Reference Number	λ mμ	log ε	Nature of band
1,5-diaryl-1,2,4-triazole-3-aldehydes:			
IVa	247	4.05	Maximum
	220	4.25	Shoulder
IVb	243	3.95	Flattened Max. 246-237
	219	4.17	Flattened Max. 221-216
IVc	246	4.05	Broad Maximum 250-236
	221	4.25	Shoulder
IVd	246	4.18	Maximum
IVe	261	4.12	Shoulder
	228	4.44	Maximum
IVf	254	4.11	Flattened Shoulder
	226	4.31	Maximum
IVg	256	4.30	Maximum
	223	4.39	Shoulder
1,5-diaryl-3-hydroxymethyl-1,2,4-triazoles:			
IIIaB	248	4.05	Maximum
	222	4.26	Shoulder
IIIb	244	4.07	Flattened Max. 249-237
	220	4.35	Flattened Max. 223-216
IIIc	248	3.96	Maximum
	224	4.15	Shoulder
IIId	246	4.17	Maximum
IIIe	261	3.93	Shoulder
	228	4.25	Maximum
IIIf	252	4.15	Shoulder
	226	4.34	Maximum
IIIg	258	4.14	Maximum
	224	4.25	Shoulder

Reference Number	λ mμ	log ε	Nature of band
1-p-tolyl-5-phenyl-3-substituted-1,2,4-triazoles:			
IIIb	As above		
IVb	As above		
XIa	250-210	4.14-4.38	smooth, slightly sloping curve
XIb	250-210	4.09-4.30	smooth, slightly sloping curve
XIc	250-210	4.18-4.32	smooth, slightly sloping curve
XXb	261	4.26	slight maxima on a near plateau
	223	4.25	270-215mμ
XVIc	240	4.18	Maximum
Intermediates:			
$VIIb_2$	234	4.19	Maximum
	281	3.75	Maximum
	342	3.93	Maximum
$VIId_1$	233	4.30	Maximum
	293	3.95	Maximum
	337	4.18	Maximum

III. The isomeric 1,5-diphenyl-3-hydoxymethyl-1,2,4-triazoles.

There were no significant differences in the chemical properties of the isomeric alcohols (IIIaA and B) (Section A,12). The isomerism could not lie in the crystal structures, as the alcohols maintained their identities in solution. A was stable in a non-polar environment, but otherwise changed readily to B. B was monomeric (Rast). A molecular weight determination on A gave a similar result; but was inconclusive, due to the probable conversion to the B-form under the experimental conditions used. From the relative positions and intensities of the OH-stretching bands in the infra-red spectra of A and B, mentioned later, it may seem possible that A is a polymer and B a monomer. Against this is the improbability of the monomeric form being more stable than the polymeric; and the observation that the A form has the lower, and not the higher, melting point.

The ultra-violet and infra-red spectra were studied, in an attempt to determine the type of isomerism present. The (IIIaA) used was a few milligram sample of the original preparation, before any (IIIaB) had been obtained. It had m.p. 128-130°C, after storage for 2 1/2 years in a stoppered tube. A later preparation of (IIIaA) had changed almost entirely to (IIIaB) within a year.

It was found that the ultra-violet spectral curve of A changed to that of B, in methanol solution, over a period of several hours (Fig.1):

Compound present	λ mμ	Nature of the band	logε
IIIaA, Initial Curve (I)	260	Maximum	3.83
	220	Slight Shoulder	4.03
Final Curve (VII) IIIaB Stable	248	Maximum	3.94
	222	Shoulder	4.13
	248	Maximum	4.05
	222	Shoulder	4.26

FIGURE 1.

Ultra-violet curves showing the conversion of the 1,2,4-triazole-alcohol (IIIaA) to (IIIaB).

Concentration: 0.015 mgm. (IIIaA) per ml. methanol.

I. Initial curve of (IIIaA) in methanol.

II. 10 minutes after mixing.

III. 2 hours " "

IV. 5 hours " "

V. 8 hours " "

VI. 23 hours " "

VII. 48 hours " "

TRANSMITTANCE
WAVELENGTH mμ
I
II and I
III
IV
V
VI
VII

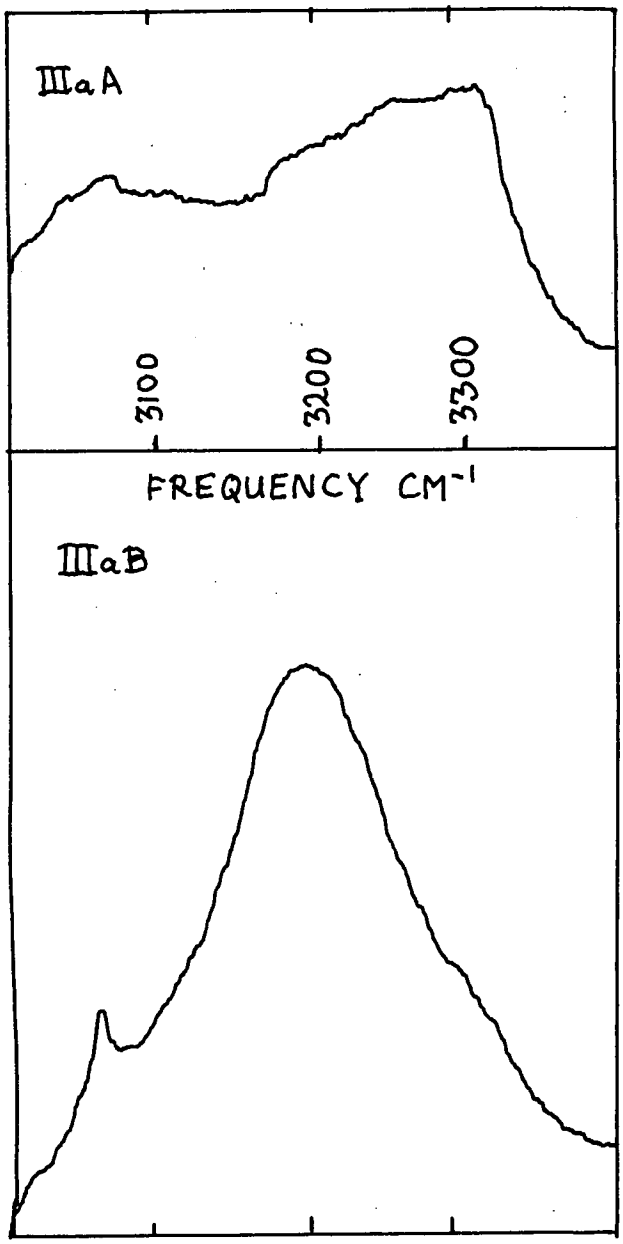


Fig. 2 OH Stretching Bands.

Fig.3. Infra-red Spectrum of (111aA) in KBr.

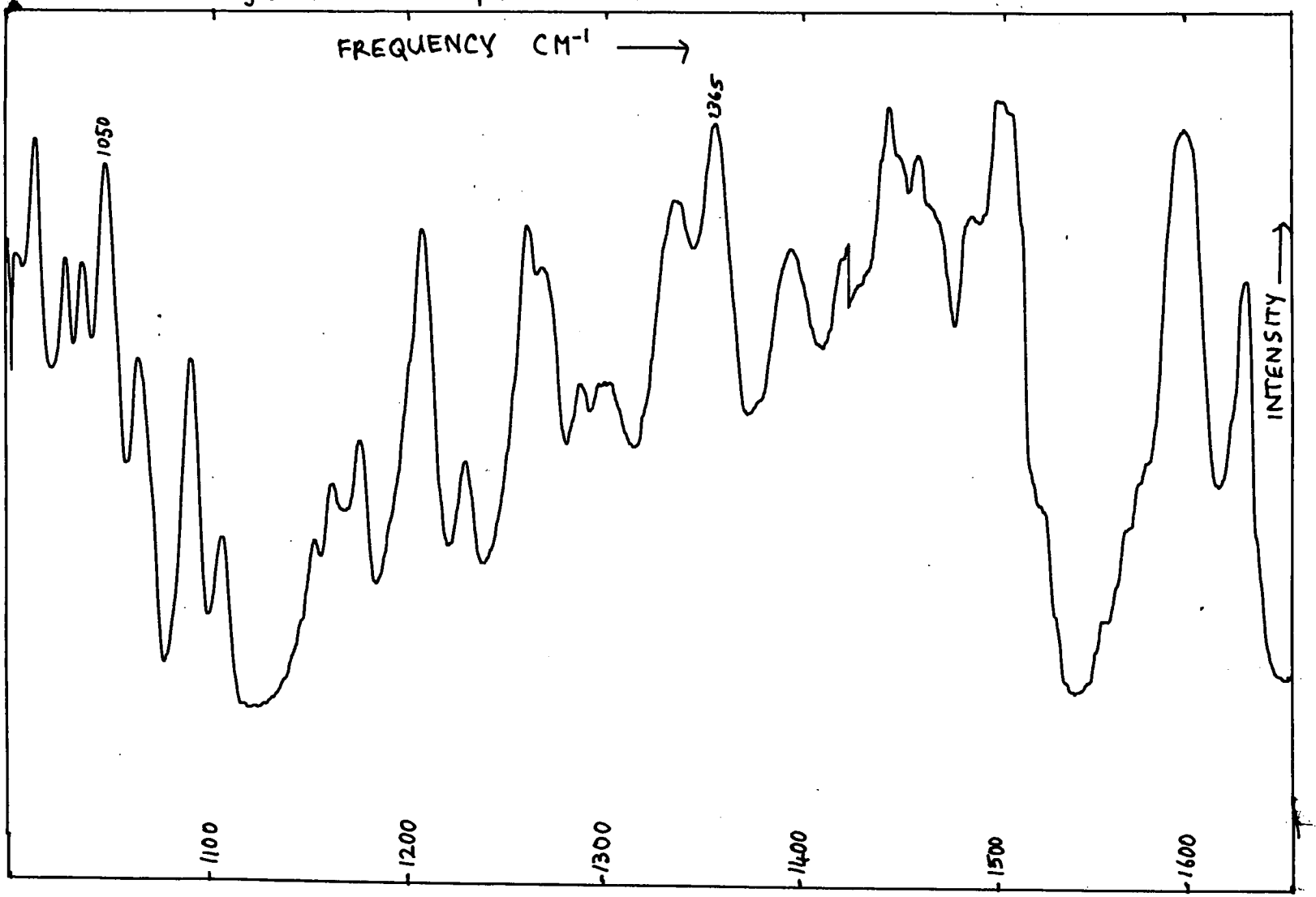
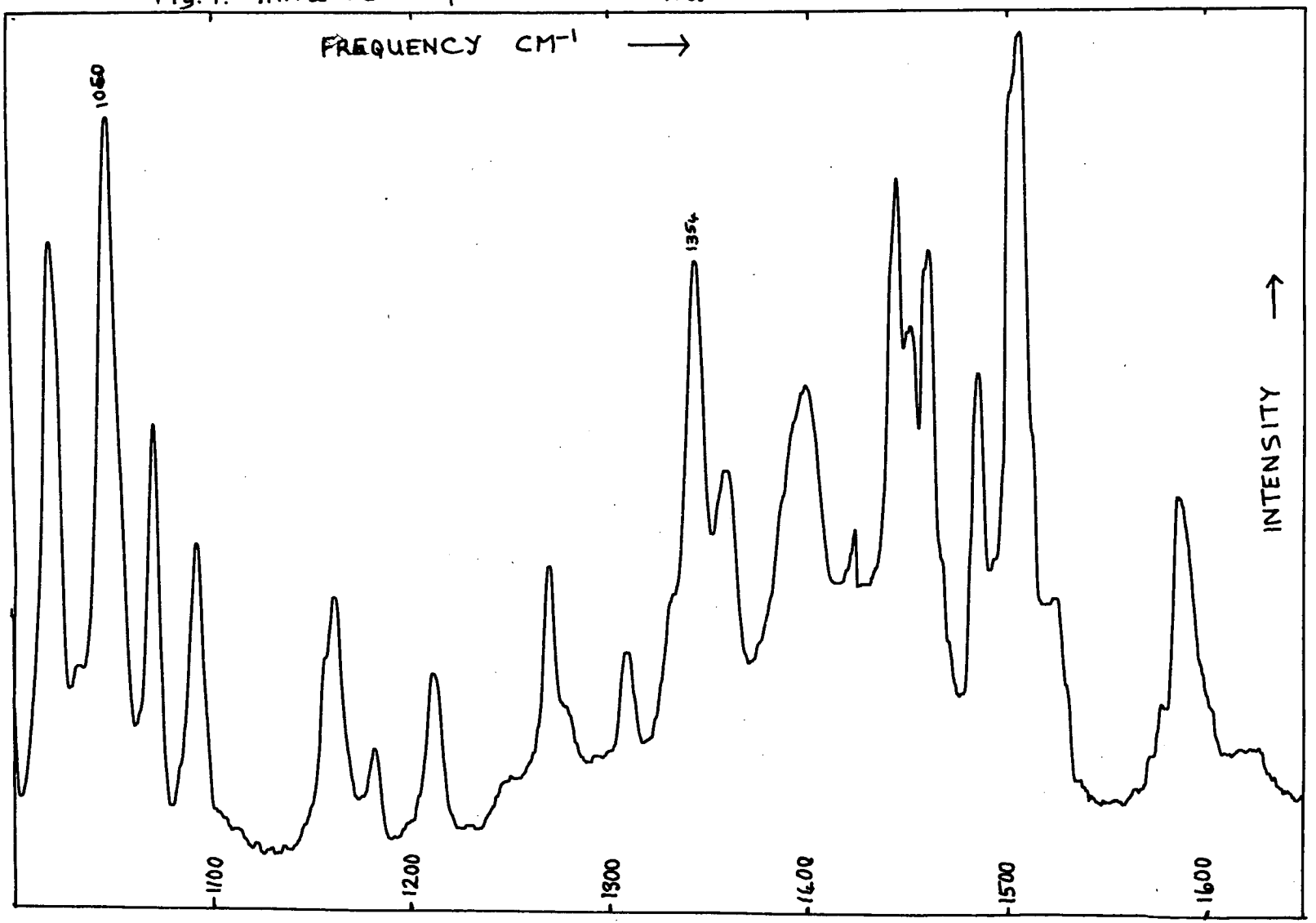


Fig.4. Infra-red Spectrum of (111aB) in KBr.



The final curve (VII), after the rearrangement of (IIIaA), had an identical shape to that of (IIIaB), although the latter had slightly higher extinction coefficients. A hyperchromic shift was present in both bands. This was slightly bathochromic in the lower band, and hypsochromic in that at longer wavelength. A shift of λ max to shorter wavelength, in a change from a labile to a stable isomer, is less common than the reverse. It has, however, been observed in the cis and trans azobenzenes (108, 110, 112). The extent of the hypsochromic shift ($\sim$12 mμ), indicates a decrease in energy of 4-5 kcals. per mole (108).

The infra-red spectra of (IIIaA and B) were determined, both in KBr discs and Nujol mulls. (IIIaA) was stable in both. Sections of the spectra in KBr are shown in figs. 2, 3 and 4. The spectrum of (IIIaB) closely resembled those of the other stable alcohols (Section E, II). Those of A and B varied in several respects.

I. Alcohol bands.

a) OH-stretching frequencies (fig. 2).

In the spectrum of B this band was strong and broad with a single peak at 3190 cm^{-1} in KBr, and 3180 cm^{-1} in Nujol. The corresponding band in the spectrum of A was almost as intense, but was much broader. The wide, irregularly flattened peak had maxima at 3300 and 3250 cm^{-1}, in both KBr and Nujol. The positions and nature of these bands indicated that hydrogen bonding was present in both compounds. The strength of this bonding is considered to increase by about one kcal. for a reduction in frequency of 35 cm^{-1} (100); and it could thus be assumed to be weaker in A than B. It also seemed possible that more than one type of hydrogen bond was present in A, as the unusual shape of this part of the curve suggested overlapping bands.

From the frequencies of the OH-stretching band in the other stable alcohols it could be deduced that the strength of the hydrogen bonding was in the order (IIIb)~(IIIe)> (IIIaB)> (IIIc)> (IIId).

b) C-O stretching and OH bending frequencies (figs 3 and 4).

The positions of these bands in (IIIaB) are given in (Section E,I.).The lower frequency band was present in the (IIIaA) spectrum at 1050 cm^{-1}, in both KBr and Nujol ; and resembled the band near 1050 cm^{-1} in all the other alcohols. The higher frequency band was at 1365 cm^{-1} in the A spectrum in KBr; but it was slightly split in Nujol, with maxima at 1362 and 1369 cm^{-1}. These frequencies were only slightly higher than those observed in the stable alcohols.

II. Other bands.

As mentioned previously, no attempt has been made to interpret in detail the background spectra of the 1,5 - diaryl-1,2,4-triazoles, including those of the alcohols. The absorption frequencies of most of the bands in the A spectrum did not differ greatly from those in that of B. There were, however, many differences in relative intensities of the bands, and especially in their width. Below 1700 cm^{-1} the bands in the B spectrum were sharp; those in that of A were frequently broader, and overlapped to a greater extent.

Each of the stable alcohol spectra , including that of (IIIaB), showed a medium to strong, not particularly sharp band, at a frequency 15-20 cm^{-1} higher than that of the alcohol band near 1350 cm^{-1}. A similar band was present in the spectra of (XXIIb) and (XXIII), and in those of many of the triazole acids, esters and aldehydes. It may reasonably be assigned to vibrations of the Ph-N-1 linkage. C-N stretching modes of tertiary aromatic amines usually absorb strongly in the range 1360-1310 cm^{-1} (100).

A similarly shaped band appears at 1345 cm^{-1} in the spectrum of (IIIaA). This frequency is 20-30 cm^{-1} lower than that observed in the other triazoles, and reverses the band position with respect to the adjacent alcohol band.

With reference to these observations an attempt has been made to give possible explanations of the isomerism observed in the alcohols (IIIaA and B). If the relative configurations of the three rings present in (IIIa) are considered, three main possibilities appear:

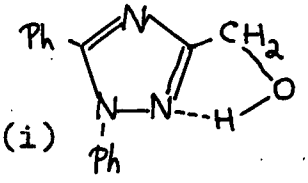
1) <u>The rings are all in the same plane.</u>

If the usual band angles are assumed this is virtually impossible, due to steric hindrance and the straim involved. In the hypothetical case the only possibility of isomerism would be that described in (2) (i an ii).

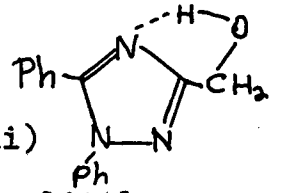
2) <u>The triazole ring is planar, and not more than one of the phenyl rings is in the plane of the heterocyclic ring.</u>

In this case the most probable situation is that where the C_5-phenyl is in the triazole plane, but may rotate as in diphenyl-, and the N_1-phenyl is directed out of the plane, also with relatively free rotation about the C-N bond. The only isomerism possible, for this type of configuration, would seem to be that shown diagrammatically in (i and ii).

(i)



(ii)



Due to the distance involved there would be little or no possibility of hydrogen bonding to N_1. There would be no steric hindrance to rotation about the C_3—C bond ; and any difference in stability of the two forms, and the strength of the hydrogen bonds, would be due to the difference in electron density on the bonding nitrogen atoms. While there are no definite figures for this, approximate calculations

indicate that the electron density might be slightly higher on N_4 than N_2 (pg.9; and refs. 5,6). If the presence of the phenyl groups does not reverse this, the formula (ii) could be assigned to (IIIaB) and that of (i) to (IIIaA). As the spectra of the other alcohols resembled that of B more closely than that of A, they would presumably also have the type of hydrogen bonding shown in (ii).

This type of isomerism is the simplest and the most obvious. There are, however, several observations which are not fully explained on this theory. These include the unusual shape of the OH-stretching band; the frequency change of the assumed Ph-N band; and the broadening of many of the bands in the infra-red spectrum of A. The energy difference present between the isomers, as shown by the shift in λ max (Fig.1), is, too, unexpectedly large for a change between two such apparently similar types of hydrogen bonding.

3) The triazole ring is not planar.

The 1,2,4-triazole ring is regarded as heteroaromatic, but considerations of the optimum bond angles indicate that strain is present, and some buckling is not unlikely. This would be increased if there were any tendency for the phenyl rings to assume a more coplanar position to each other. This effect could not be complete; and from a steric viewpoint the phenyl groups would still be "transoid" to each other, with respect to the imaginary original plane of the triazole ring. The aryl groups are too large for a significant probability of the "cisoid" form.

The 3-CH_2OH group could then be either "cisoid" or "transoid" to the Ph-C's group. In both cases, even with much buckling of the triazole ring, there would be still relatively free rotation about the C_3-C bond.

If "transoid", the possibilities of hydrogen bonding are, as in (2), to N_2 and N_4 only. Distance, and steric hindrance by the Ph-N< group, would prevent any interaction with N_1. If the difference in electron density between N_2 and N_4 were not great the probability of the forms (i) and (ii) would be comparable, the energy differences slight, and no split in an alcohol spectral band be observed.

If the $-CH_2OH$ side chain were "cisoid" to Ph-C⁵ such bonding to N_2 and N_4 would also occur. In this case, however, there could be the additional possibility of hydrogen bonding to N_1, if the triazole ring were sufficiently twisted. The length of such a bond would be greater than that to N_2 or N_4, but this effect might be partly offset by the greater stability of the six-membered ring formed (110).

This hypothesis is more consistent with the spectral evidence, than is that in (2). The order of the energy change occurring in the A to B conversion is consistent with a change from a "cisoid" to a "transoid" form. The presence in A of hydrogen bonds of different strengths, but weaker than those in B, could explain the shape and relative position of the OH-stretching band in the A spectrum. Differences in energy of the two types of bonding could be the cause of the split in the 1362/9 cm^{-1} band in the A spectrum in Nujol; but would not explain the single peak in the KBr preparation.

The frequency shift in the band near 1570 cm^{-1}, assumed due to the Ph-N<^{1} band, is more explicable if there is bonding to this nitrogen atom, than if only N_2 and N_4 are concerned.

On the evidence reported in this thesis hypothesis (3) might be favoured, despite ones' prejudice against the buckling of a small heteroaromatic ring. Further evidence, e.g. X-ray diffraction data, will be required to arrive at a fully satisfactory conclusion.

Appendix A.

Appendix A: Nitrogen analyses in the 1,2,4-triazole series.

Accurate nitrogen analyses in many aza-heterocyclic compounds may be difficult to obtain by conventional analytical methods (2,14,19,97,98,99); and specially modified procedures may be necessary in individual cases. This has also been observed with 1,2,4-triazoles, where nitrogen analyses tend to be consistently too low.

The statement of Potts (66) that "failure to obtain satisfactory analytical figures can be attributed to contamination with small amounts of by-products having the same chemical properties," would seem rather too sweeping. While undoubtedly a factor, the presence of impurities should also give spuriously high values; and the average error should be independent of the nature of the triazole.

In the course of this work it has been observed that the accuracy of the nitrogen analyses, for 1,2,4-triazoles, which analyse satisfactorily for other elements present, is partly dependent on the method of analysis used, and the structure of the triazole itself. Due to technical limitations nearly all nitrogen analyses were done by the conventional Dumas micromethod (see Acknowledgments), which is known to give low values if the nitrogen is tightly bound (19,97,98,99). The results of nitrogen determinations, by this method, in 76: 1,2,4-triazoles, all first synthesised during this investigation, are summarised in (Table VII). The average deviation in all cases was on the negative side.

For the N-unsubstituted compounds the accuracy of the determinations was satisfactory, the average error being less than 1%. Potts' statement may refer only to this type of triazole as his published work in this field

is limited to the 3,5-diaryl or 3,5-aryl-alkyl-1,2,4-triazoles (46,65).

In the case of N-aryl-substituted-1,2,4-triazoles this method still usually gave results within acceptable limits when C,H,N,O were the only elements present. However the average error (-1.5%) was just double that observed with the N-unsubstituted-triazoles (-0.75%). This difference was doubtless due to the greater difficulty of liberating nitrogen tightly bound to an aryl group.

The unmodified Dumas procedure was unsatisfactory for the analysis of N-aryl-1,2,4-triazoles containing bromine, the average negative deviation being 6.9%. Most of the absolute nitrogen values found in this class of compounds were more than 0.7% too low. This tendency of bromine to interfere with nitrogen determinations, particularly in heterocyclic compounds, is well known (14,97). Special analytical methods, involving the addition of oxidising agents or high reaction temperatures, are often necessary. Such very low nitrogen values were also occasionally observed with N-aryl-triazoles containing $-NO_2$, $-C(=O)-NHNH_2$, or other nitrogenous side chains.

Unfortunately it was not possible to have most of these compounds analysed by more suitable methods. Dr. Challen (see Acknowledgments) did nitrogen determinations on two such samples which had previously been analysed by the unmodified Dumas micromethod (A). The method used was that of Spies and Harris (98), using potassium chlorate (D).

	Nitrogen values %		
Compound	Theoretical	Method A	Method B
XIIIc	25.92	24.65	25.69
XVc	19.55	18.42	19.40

It seems that for some N-aryl-1,2,4-triazoles the modification (B) gives more accurate nitrogen values, and is the method preferred.

TABLE VII Nitrogen analyses on 1,2,4-triazoles.

Dumas micromethod.

Nature of 1,2,4-triazoles analysed	Number	Average nitrogen %			Average % deviation
		Theoretical	Found	Difference	
N-unsubstituted	20	24.91	24.72	-0.19	-0.75
1,5-diaryl-3-substituted. Not containing bromine	49	18.29	18.01	-0.28	-1.5
1,5-diaryl-3-substituted. All containing bromine	11	14.98	13.99	-0.99	-6.9
All 1,5-diaryl 3-substituted	96	17.64	17.22	-0.42	-2.4
All triazoles	76	19.55	19.19	-0.36	-1.85

Appendix B.

Appendix B: N-bromo-diacylamines.

R_2NH (XLIV) a.R = $-C(=O)-CH_3$

b.R = $-C(=O)-CH_2CH_3$

R_2N-Br (XLV) c.R = $-C(=O)-Ph$

Many N-bromo-amides or cyclic imides, such as N-bromo-acetamide or N-bromo-succinimide, are known. They are of varying stability and are usually strong brominating agents. Isolation of N-brominated-acylic diacylimines had been unsuccessful. Bromination of diacetimide (XLIVa) in dry ether gave an acrid oil, which slowly precipitated salt-like crystals, containing no positive bromine. The analysis and properties of this compound were consistent with the formula

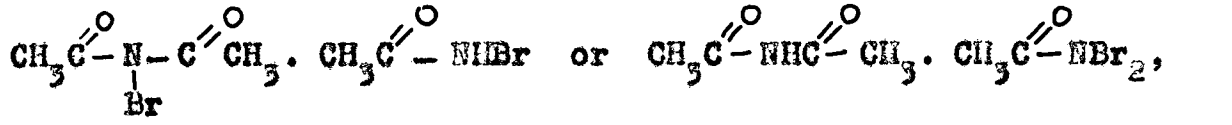
$$CH_3C(=O)-NHC(=O)-CH_3 . NH_4Br \quad (43).$$

Its formation, as described, was confirmed. No compounds containing positive bromine were isolated on attempted bromination of (XLIVa or b) by standard methods, using alkalies and free bromine.

An apparent exception was the reaction of diacetimide with bromine in aqueous sodium bicarbonate, when an unstable compound (P) containing much positive bromine, was isolated. Inorganic material present could not be completely removed, and analytical data were only approximate. The same compound formed by a similar bromination of the adduct

$$CH_3C(=O)-NHC(=O)-CH_3 . CH_3C(=O)-NH_2,$$

which suggested that the product was also an adduct. Possible formulae, consistent with the analyses, are



if N-bromination is assumed.

Dipropionimide (XLIVb), which is more stable than diacetimide, and does not form an adduct with propionamide, was not brominated under these conditions. The use of excess bromine did not alter the composition of (P), which also formed in low yield when a chloroform solution of (XLIVa) was treated with aqueous bromine. (P) rapidly converted aniline to 2,4,6-tribromo-aniline. With toluene (P) produced small amounts of benzyl bromide, identified as its iso-thiouronium picrate.

Both diacetimide and dipropionimide were successfully N-brominated when shaken in chloroform with an excess of freshly prepared aqueous hypobromous acid. The products were very unstable, and it was difficult to obtain accurate analyses as delays of several days were often involved. The analyses and properties agreed with the structures (XLVa and b), although O-bromination could not be entirely excluded.

Dibenzimide (XLIVc) gave only a trace of brominated product when treated with hypobromous acid. Reaction with bromine in aqueous KOH gave a reaction product containing about one-third the positive bromine expected in (XLVc). (XLVa) behaved like N-bromo-acetamide or N-bromo-succinimide in bromination reactions, but was much less stable. There was an immediate vigorous reaction with anthracene to give a product which appeared to be crude 9-bromo-anthracene. Phenanthrene gave a complicated mixture of products when it was heated with (XLVa) in CCl_4. The reaction of (XLVa) with aniline or toluene was the same as that of (P). There was no proved bromination

of benzene with (XLVa), and with pyridine only its HBr salt was isolated.

Pure (XLVa) could not be made by the action of bromine in chloroform on Na-diacetimide. The product contained about 60% of the positive bromine, theoretically present in (XLVa), and unchanged (XLIVa). (XLVa) breaks down at a regular rate when exposed to the air, probably due to hydrolysis, and free diacetimide is obtained. The N-bromo-diacylimines may be preserved for several weeks at 0°C. in a vacuum desiccator.

Experimental:

N-bromo-diacetimide (XLVa)

An approximately 1% solution of hypobromous acid was prepared by shaking together bromine (16 g.) and mercuric oxide (11 g.) in water (1 L.) for 10 minutes. The solution was filtered and used at once.

Diacetimide (21,43,62) (6.0 g.) in chloroform (200 ml.) was shaken for a total of 30 mins. with aqueous hypobromous acid (1%, 1300 ml., in 2 portions). The aqueous layer was further extracted with chloroform (2 x 50 ml.), the chloroform solutions combined, dried over $CaCl_2$, and evaporated to dryness in vacuo. The residue was an orange, acrid and lachrymatory oil (9.8 g., positive bromine: 37%), which was partially solidified by cooling in liquid nitrogen for a few minutes. The mushy material was then spread thinly on a porous plate, and kept in a vacuum desiccator over KOH/$CaCl_2$/paraffin chips, in a refrigerator at 0-4°C. After 2-4 hours the white solid residue (2.4 g., 22%), had m.p. 27-31°C.

(Found: C, 25.8; H 3.4; N, 7.6; Total Br, 44.8. $C_4H_6NO_2Br$ requires C, 26.7; H, 3.4; N, 7.8; Total and positive Br, 44.4%).

Positive bromine: 44.4, 44.2, 44.1, 44.4%, on different samples.

After 24 hours in a loosely stoppered tube, at room temperature, positive Br, 41.9%. After 4 days this had dropped to 38.4%, and after 8 days to 34.5%. (XLVa) melted to a clear, colourless liquid, which on further heating went deep orange, and decomposed with gas evolution $>150^{o}C$. It decomposed instantaneously in water, and very rapidly in damp solvents. In several cases, where other compounds present had been brominated, free diacetimide was isolated from the reaction mixture.

N-bromo-dipropionimide (XLVb).

Dipropionimide (63) (4.0 g.) in chloroform (150 ml.) was shaken for 30 minutes with cold, freshly prepared, aqueous hypobromous acid (800 ml., in 3 portions). The aqueous layer was extracted with chloroform (2 x 30 ml.), the chloroform solutions combined, dried over anhydrous sodium sulphate, and evaporated to dryness in vacuo. The residual acrid oil was spread on a porous plate and kept in a vacuum desiccator over KOH/silica/paraffin chips. After a few hours the white crystals (4.4 g., ~69%) had m.p. 60-72°C. Solution in dry, cold, chloroform, filtration and evaporation of the solvent under vacuum in the cold, gave colourless, transparent crystals, collapsing to a white powder, m p. 73-8°C. A sharper melting point could not be obtained. On further heating, the clear liquid went deep orange and decomposed with gas evolution $>150^{o}C$.
(Found: C, 35.6; H, 4.8; N, 6.2; Total Br, 36.3; O, 16.0; $Cl_1 < 0.5$; Positive Br, 35.6, 35.7%.
$C_6H_{10}NO_2Br$ requires C, 34.7; H, 4.8; N, 6.7; O, 15.4; Total and positive Br, 38.4%.)

Decomposition of (XLVb) in water was very rapid, though less so than with (XLVa). When (XLVb) was gently heated in ethanol for 2-3 minutes the solution rapidly went deep orange, there was a vigorous evolution of acrid fumes, and on cooling pure dipropionimide precipitated.

Bromination of diacetimide with bromine in aqueous sodium bicarbonate.

Diacetimide (10 g.) was dissolved in a solution of sodium bicarbonate (7.5 g., 1:1) in water (110 ml.), and the solution cooled in an ice salt bath. Bromine (15.8 g., 1:1) was added dropwise with good stirring. CO_2 was evolved, and a thick, yellow paste formed within a few minutes. After 30 minutes the mixture was filtered rapidly on a Büchner filter, washed with a little ice water, and sucked dry. The product was spread on a porous plate in a vacuum desiccator over KOH/silica/paraffin chips. After 2 hours the sticky, orange crystals (6 g.) were dissolved in cold, dry chloroform, filtered, and the solvent largely evaporated. The dry, pale yellow powder obtained had m.p. 118-9°C. (5.1 g.) (P). The melting point varied with different preparations, from 110-3°C. to 120-2°C. Inorganic matter, identified as almost entirely sodium bromide, was always present in amounts of 10-16%. This variation suggested that this was a mechanical impurity, and that the NaBr was probably not bound in stoichiometric proportions.

Analyses:

Found: C, 14.7; H, 2.2; N, 5.7; Total Br, 60.4; Positive Br, 47.8; Ash ~ 16%.

Assuming the ash is all NaBr as a mechanical impurity, these figures become: C, 17.5; H, 2.6; N, 6.8; Total Br, 57.2; Positive Br, 56.9%.
$C_6H_9N_2O_3Br_3$ requires C, 18.1; H, 2.3; N, 7.1; Total and positive Br, 60.4%.
On a different sample: Positive Br, 50.4; ash, 12.8. Corrected positive Br, 57.8%.

Bromination of an approximately 1:1 acetamide/diacetimide adduct (21) (2.2 g.) with bromine/aqueous $NaHCO_3$, as described above, gave a yellow powder (1.1 g.) m.p. 117-9°C. The mixed m.p. with a sample prepared by diacetimide bromination (m.p. 120-2°C.) was 117-121°C. This appeared to be the same compound. It contained 13% ash; positive Br, 50.5; corrected positive Br, 58.1%.

SUMMARY

1. Synthetic methods for the preparation of 1,2,4-triazole-C-aldehydes have been investigated. Seven 1,5-diaryl-1,2,4-triazole-3-aldehydes and their derivatives have been prepared from the corresponding alcohols, or carboxylic acid derivatives.

2. The 3-substituted-1,5-diaryl-1,2,4-triazoles, required as starting materials, were prepared from the alkaline rearrangement of 4-arylazo-oxazolones. The scope and mechanism of this rearrangement was studied. Several of the products were converted to triazoles containing other functional groups.

3. Five N-unsubstituted-1,2,4-triazole-3-aldehyde dimethyl acetals were synthesised by condensation of imino ethers with dimethoxyacethydrazide. Each was converted to the aldehyde 2,4-dinitrophenylhydrazone. The condensation was extended to the preparation of triazoles containing other 3-substituents.

4. The ultra-violet and infra-red spectra of many 1,5-diaryl-3-substituted-1,2,4-triazoles, including the aldehydes, have been determined.

5. Spectral evidence was used to study the structures of the isomeric 1,5-diphenyl-3-hydroxymethyl-1,2,4-triazoles.

More extended investigations on the spectra of 1,2,4-triazoles are in progress in this department. Additional studies are necessary to determine the conditions suitable for the formation and isolation of the N-unsubstituted-1,2,4-triazole-3-aldehydes, by cleavage of their acetals. Further work on the chemical properties of the 1,2,4-triazole-aldehydes, already obtained, is indicated.

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I wish to express my appreciation to my supervisor, Dr. J.B.Polya, for his helpful discussions and generous assistance during the course of this project.

Microanalyses were performed by Dr. K.W.Zimmermann, at the Australian Microanalytical Service, C.S.I.R.O., Melbourne. Additional nitrogen analyses (Appendix A) were kindly done by Dr. E.Challen, of the Microanalytical Laboratory, University of New South Wales. The infra-red and ultra-violet spectra, discussed in Section E, were determined by Mrs. O Tavendale, of this department. Many of the results could not have been obtained without their assistance.

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